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ISTITUTO NAZIONALE DI OTTICA

CONSIGLIO NAZIONALE DELLE RICERCHE

Workshop on

Advanced Medical Imaging with Synchrotron and Compton X-ray Sources

Bologna, 21-22 November 2019

Laser-driven particle and photon sources for medical applications at ILIL-CNR

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1 Intense Laser Irradiation Laboratory
Consiglio Nazionale delle Ricerche
Istituto Nazionale di Ottica
Sezione di Pisa, Italy

2 ***Consiglio Nazionale delle Ricerche***
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Pisa, Italy

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3 ***Azienda Ospedaliero-Universitaria Pisana***
Pisa, Italy

INFN

**Also at Istituto Nazionale di Fisica Nucleare, Sezione di Pisa, Italy*

www.ino.cnr.it

The ILIL (*Intense Laser Irradiation* Laboratory) group

PEOPLE

- Leonida A. **GIZZI*** (Resp.)
- Fernando **BRANDI**
- Gabriele **CRISTOFORETTI**
- Petra **KOESTER**
- Luca **LABATE***
- Lorenzo **FULGENTINI**
- Federica **BAFFIGI** term
- Paolo **TOMASSINI** term
- Sanjeev **KUMAR** postdoc
- Daniele **PALLA** postdoc
- Davide **TERZANI** postdoc
- Gianluca **VANTAGGIATO** undergraduate
- Federico **AVELLA** undergraduate
- Antonio **GIULIETTi** associated

*Also at INFN

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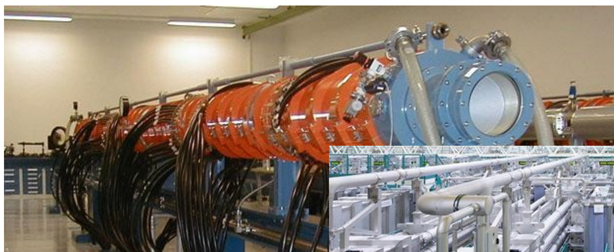
http://ilil.ino.it

Main activities and lab

Laser-plasma interactions in regimes relevant to Inertial Confinement Fusion* (Fast and Shock ignition)

- Laser-driven instabilities
- Diagnostics of ICF-relevant plasmas



PALS laser (Prague, CR)

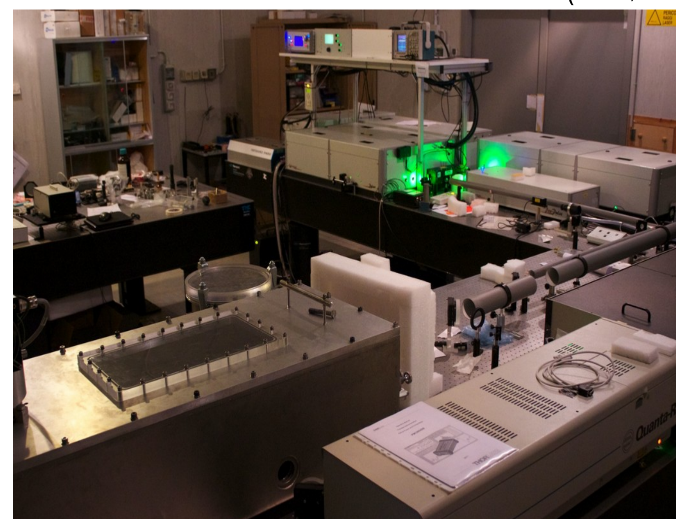
LMJ laser (Bordeaux, FR)

Typical laser figures:
Energy ~100J – 1MJ
Pulse duration: ~ns (down to 10s of ps)
Typical power: ~1TW - 1PW
Footprint: ~100s meters

Laser-driven particle accelerators

- **Electrons acceleration and X-rays radiation sources**
- Protons/light ions acceleration

ILIL-INO-CNR laser front-end (Pisa, IT)

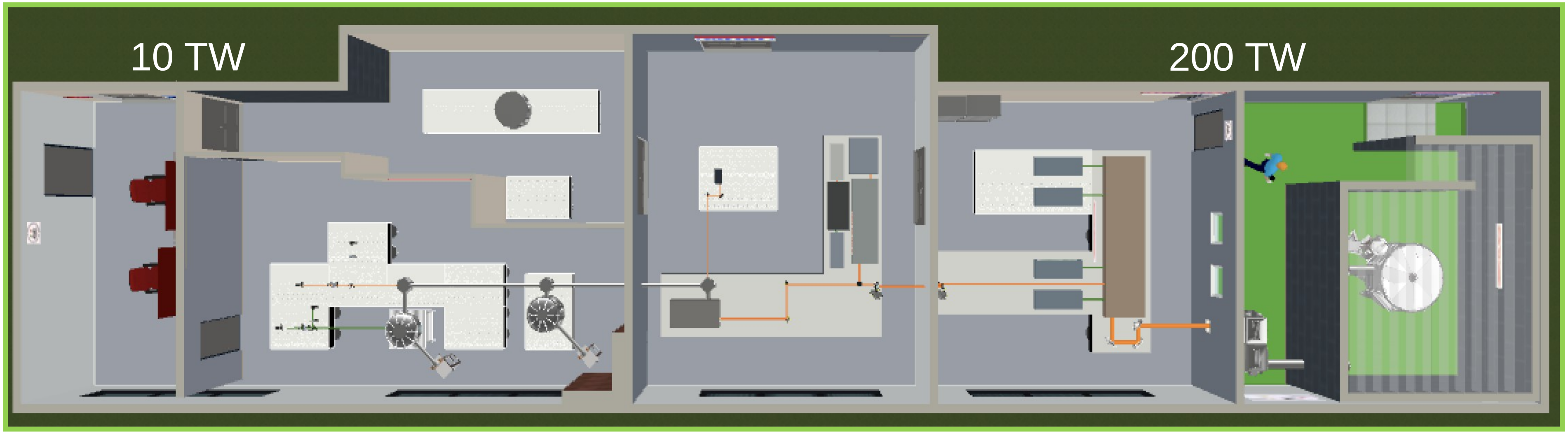


Typical laser figures:
Energy ~100mJ – few J
Pulse duration: ~10fs
Typical power: ~10TW - 1PW
Footprint: "table-top"

*Also through LASERLAB access to Laser facilities (RAL-CLF(UK), PALS (CZ) and within EURATOM Collaboration)

The *Intense Laser Irradiation Lab (ILIL)*

Major laser/lab upgrade carried out in 2017-2018, aimed at reaching the 200TW laser power level
Brand new Target Area with radiation shielding for very high energy particles built



Control room | TW Target Area | Front end | Power Amplifier | Shielded T.A.

Up to 2017 → Operational since 2018

The ILIL lasers: 200TW upgrade

Parameter	10TW (2016)	Current (mid 2019)	Final
Final amplifier pump energy	- (final amp: 2J)	15J	20J
Pulse duration	~40 fs	25 fs	25 fs
Energy before compression	0.6 J	6J	7.5J
Energy after compression	0.45 J	>4 J	>5J
Rep rate	10 Hz	1 Hz (up to 2Hz)	1 Hz (up to 2Hz)
Max intensity on target	$2x10^{19}$ W/cm^2	$>10^{20}$ W/cm2	$>4x10^{20}$ W/cm^2
Contrast (ns)	$>10^9$	10^9	10^9

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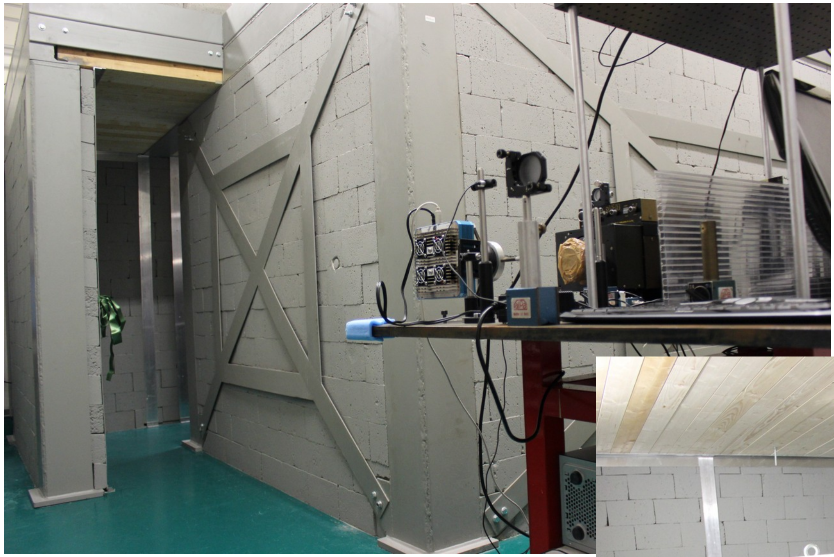
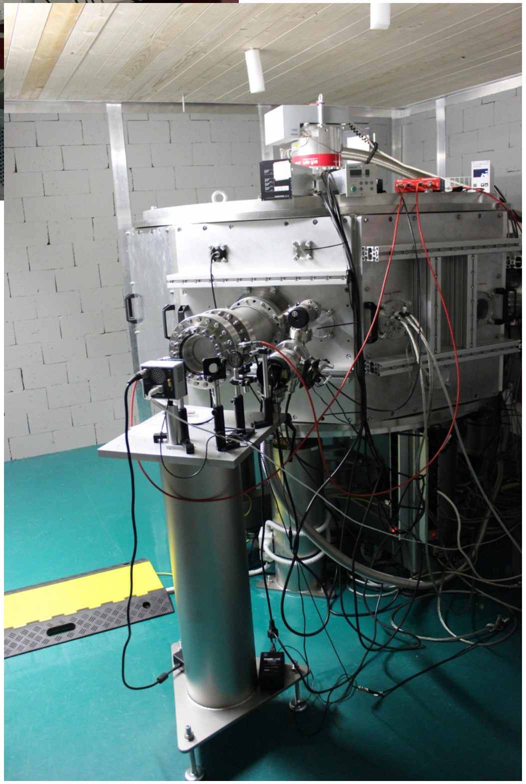
The lab: the 200TW Target Area

Target Area with radiation shielding inaugurated on March 2018





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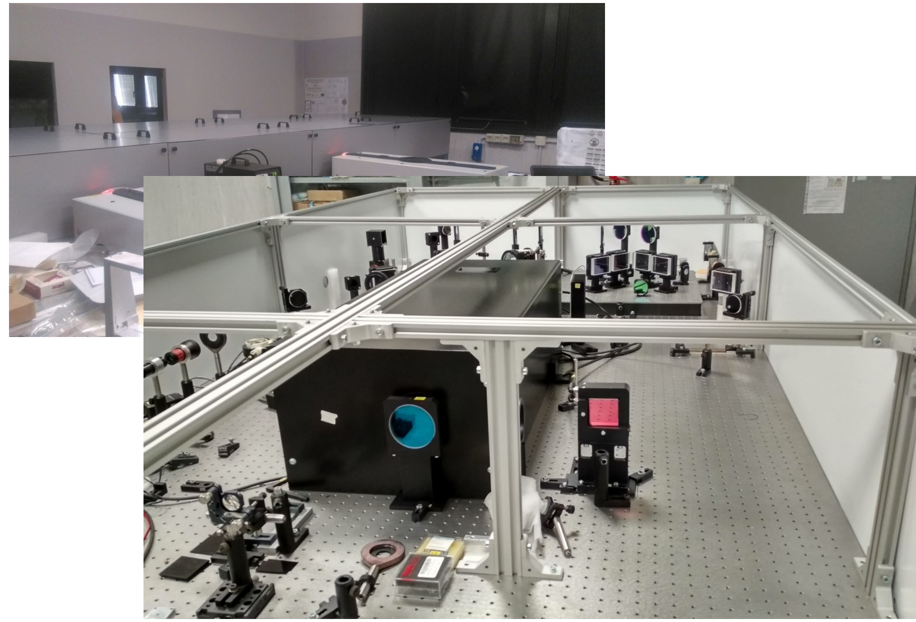
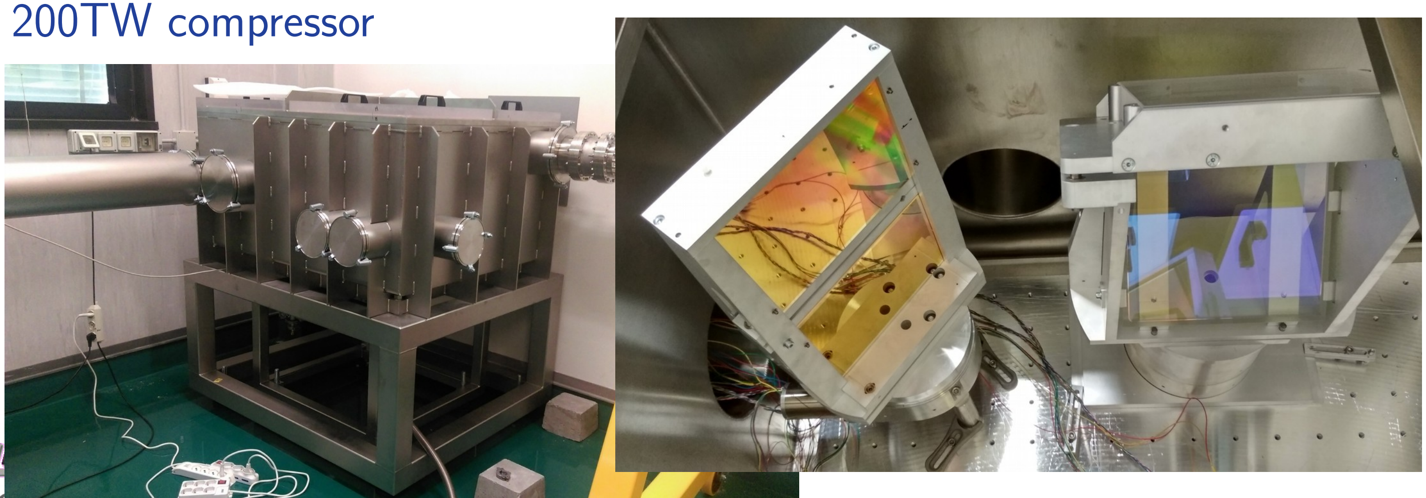
The lab: the laser system

Front-end and 10TW compressor

ILIL 200TW final amplifier (8J)



200TW compressor



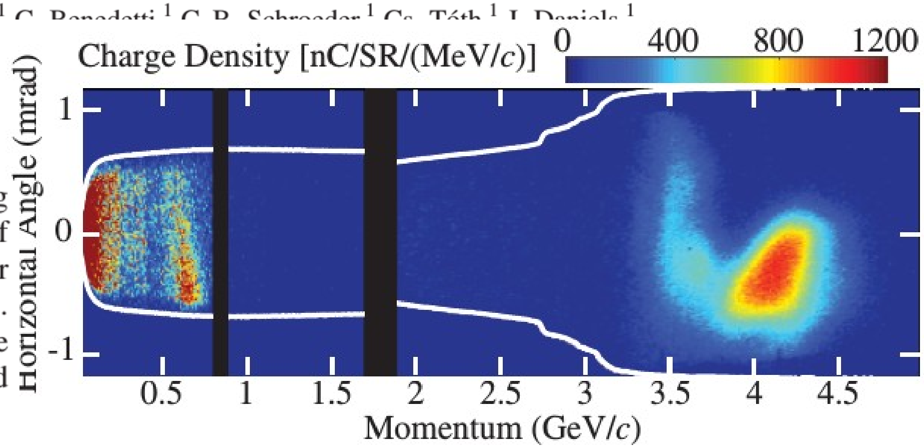
Starting point: the emerging field of *laser-driven* electron acceleration

Selected for a Viewpoint in *Physics*
PRL **113,** 245002 (2014) PHYSICAL REVIEW LETTERS week ending 12 DECEMBER 2014

Multi-GeV Electron Beams from Capillary-Discharge-Guided Subpetawatt Laser Pulses in the Self-Trapping Regime

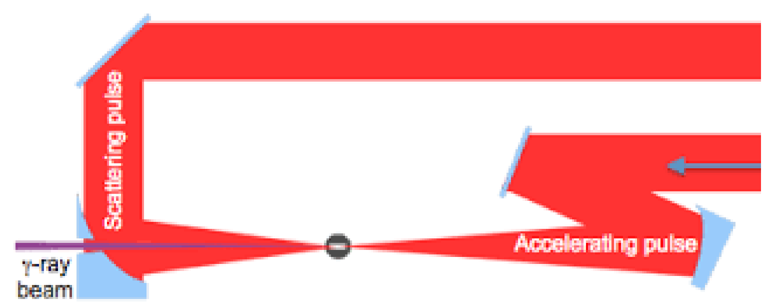
W. P. Leemans,[1,2,*] A. J. Gonsalves,[1] H.-S. Mao,[1] K. Nakamura,[1]
D. E. Mittelberger,[2,1] S. S. Bulanov,[2,1] J.-L.
[1]*Lawrence Berkeley National Laboratory,*
[2]*Department of Physics, University of Califor*
(Received 3 July 2014; revised manuscript received 11

important. In this Letter, experimental results and supporting numerical modeling are presented on the generation of electron beams with an energy of 4.2 GeV using 16 J of laser energy, significantly lower than previous experiments [8]. This was achieved by coupling laser pulses with high mode quality to preformed plasma channel waveguides produced by a 9-cm-long capillary discharge.



"Laser-driven" electron acceleration has been established up to the GeV level (now aiming at 10GeV)

The e-beam quality (increasingly "good") makes it possible to aim at secondary "all-optical" X/γ-ray sources (not relying on RF cavity accelerators)



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- A very short introduction to laser-driven electron acceleration
- Electron acceleration experiments for direct e-beams applications in medicine (radiotherapy)
  - Low-energy beams: Intra-Operatory Radiation Therapy (IORT)
  - Very-High Energy Electrons (VHEE):

    Motivations: Laser-driven VHEE sufficiently mature to possibly open up new frontiers in radiotherapy protocols

    Preliminary steps toward "real" biomedical applications: Demonstration of Intensity Modulation and Multiple-Field irradiation
- All-optical advanced X-ray sources: a compact platform for 4D microCT of small animals
- Summary and conclusions

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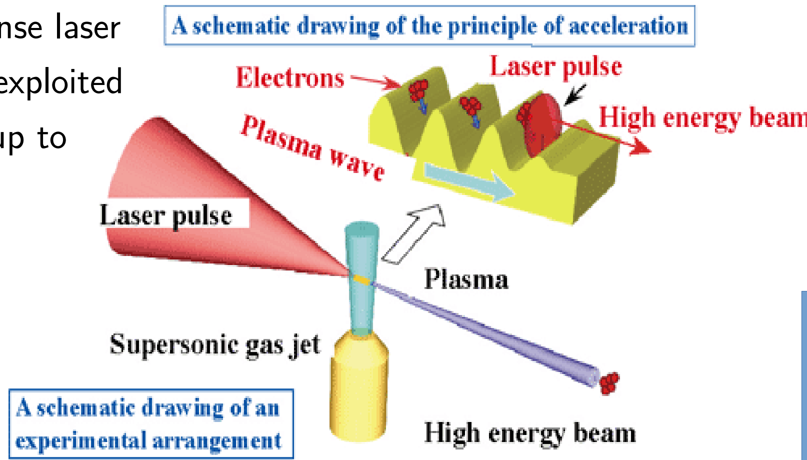
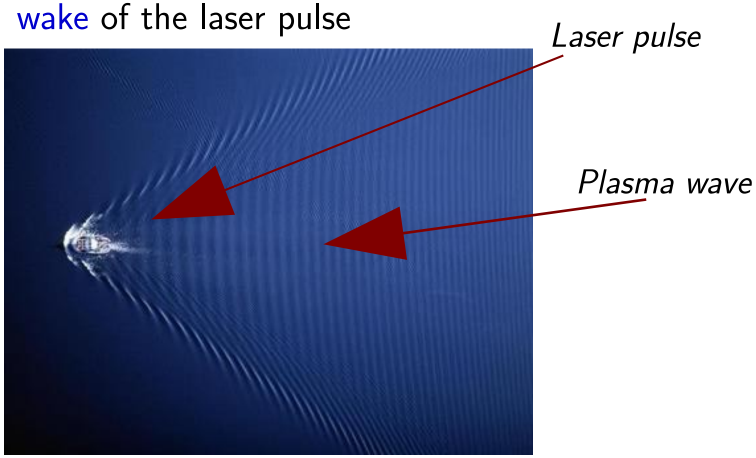
Laser-driven acceleration: the *Laser Wake-Field Acceleration* process

Ultrashort and ultraintense laser pulses can be fruitfully exploited to accelerate electrons up to relativistic energy

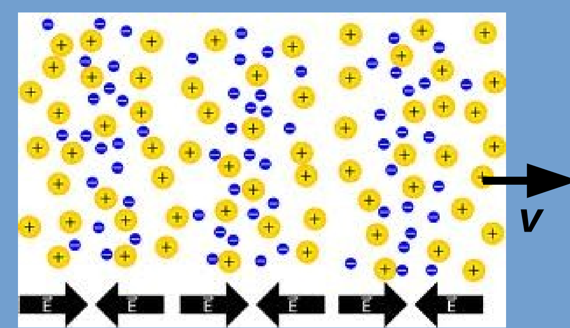


The basic ingredients:

1. Excite a plasma wave in the wake of the laser pulse



Electron plasma wave



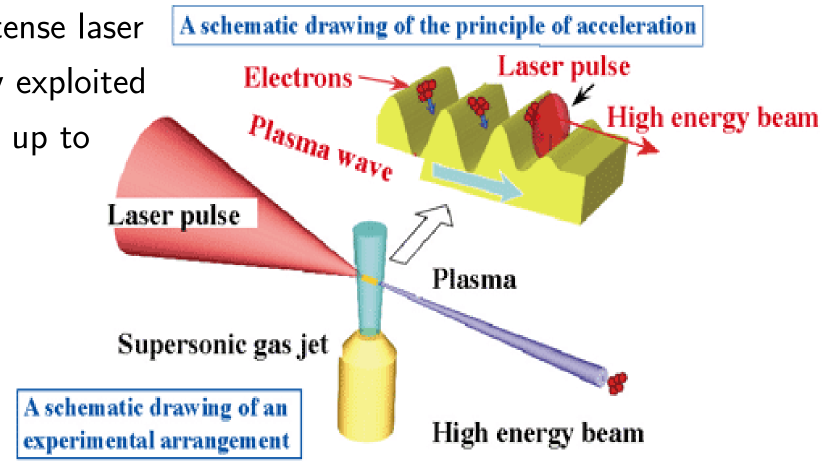
Longitudinal wave → longitudinal electric field

The wake turns out to have

$$v_{phase}^{(wake)} \simeq v_{group}^{(laser)} \simeq c$$

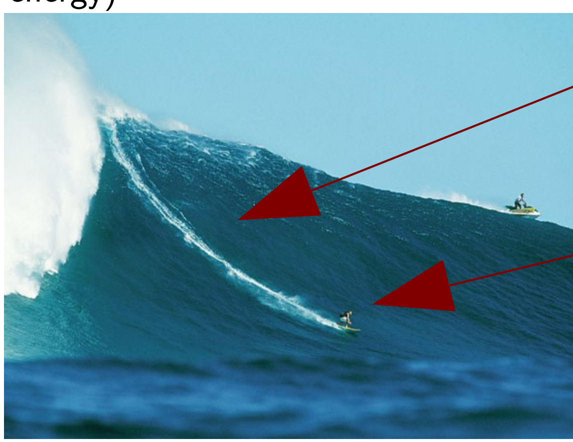
Laser-driven acceleration: the *Laser Wake-Field Acceleration (LWFA)* process

Ultrashort and ultraintense laser pulses can be fruitfully exploited to accelerate electrons up to relativistic energy

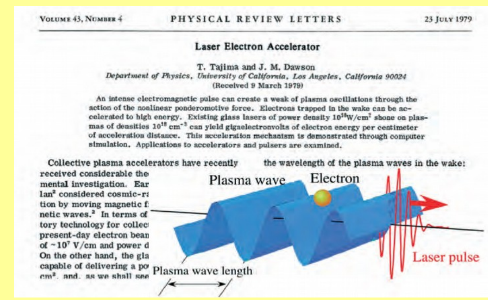


The basic ingredients:

2. Let some electrons "surf" the wave (get injected into the right phase of the wake and gain energy)



***1979**: proposal by Tajima&Dawson*



Volume 43, Number 4 — PHYSICAL REVIEW LETTERS — 23 July 1979

Laser Electron Accelerator

T. Tajima and J. M. Dawson

Department of Physics, University of California, Los Angeles, California 90024

(Received 9 March 1979)

An intense electromagnetic pulse can create a weak of plasma oscillations through the action of the nonlinear ponderomotive force. Electrons trapped in the wake can be accelerated to high energy. Existing glass lasers of power density 10^{18}W/cm² shone on plasmas of densities 10^{18} cm^{-3} can yield gigaelectronvolts of electron energy per centimeter of acceleration distance. This acceleration mechanism is demonstrated through computer simulation. Applications to accelerators and pulsers are examined.

The amplitude of the excited wave depends on the pulse length → need for ultrashort laser pulses

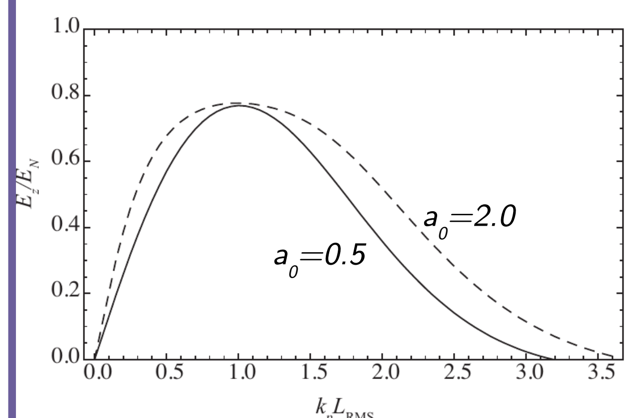


Figure credit: E.Esarey *et al.*, Rev.Mod.Phys. **81**, 1229 (2009)

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The LWFA process: maximum accelerating field

The maximum electric field amplitude is given by the wave-breaking limit, which in the relativistic case can exceed by several times the non-relativistic one

$$E_{WB} = \sqrt{2}(\gamma_p - 1)^{1/2} E_0$$

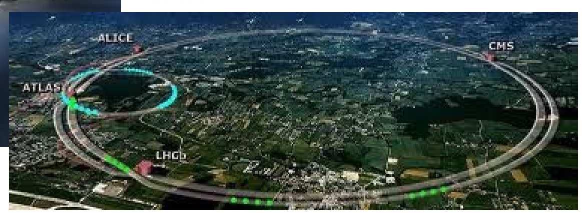
$\gamma_p \simeq \omega/\omega_p$ *(phase velocity ~ laser pulse group velocity)*

$E_0 = c m_e \omega_p / e$ *(cold, non-relativistic limit)*

Example: $n_e = 10^{17}$ cm^{-3}, $\lambda = 1 \mu m$, $E_{WB} = 14\ E_0$

$E \sim$ 300 GV/m (for 100% density perturbation at $n \sim 10^{19}$ cm^{-3})

To be compared with **classical (RF-based) accelerators limits**



- ✓ Maximum E-field ~few tens of MV/m (due to breakdown)
- ✓ Synchrotron radiation losses → ***large radius***

The LWFA mechanism allows electron acceleration up to relativistic energy to be obtained over cm-scale acceleration lengths

→ ***table-top accelerators***

LETTERS

GeV electron beams from a centimetre-scale accelerator

W. P. LEEMANS[1*†], B. NAGLER[1], A. J. GONSALVES[2], Cs. TÓTH[1], K. NAKAMURA[1,3], C. G. R. GEDDES[1], E. ESAREY[1*], C. B. SCHROEDER[1] AND S. M. HOOKER[2]

nature physics | VOL 2 | OCTOBER 2006 | www.nature.com/naturephysics

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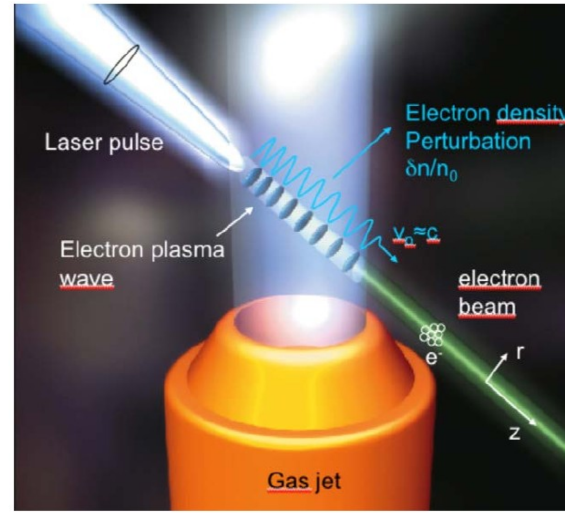
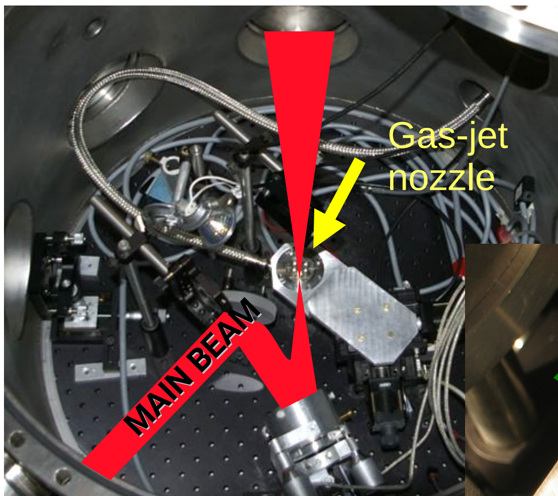
A closer look at a LWFA "accelerator"

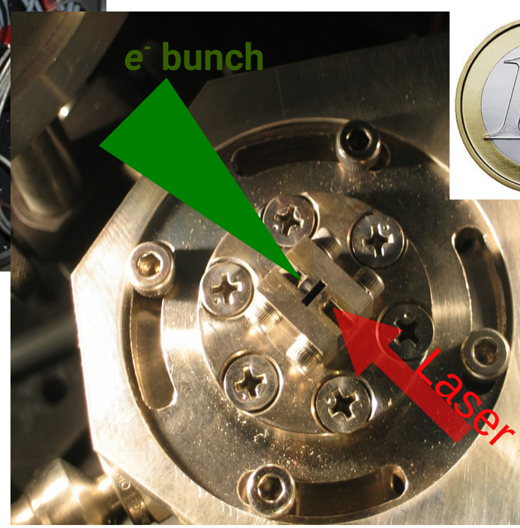


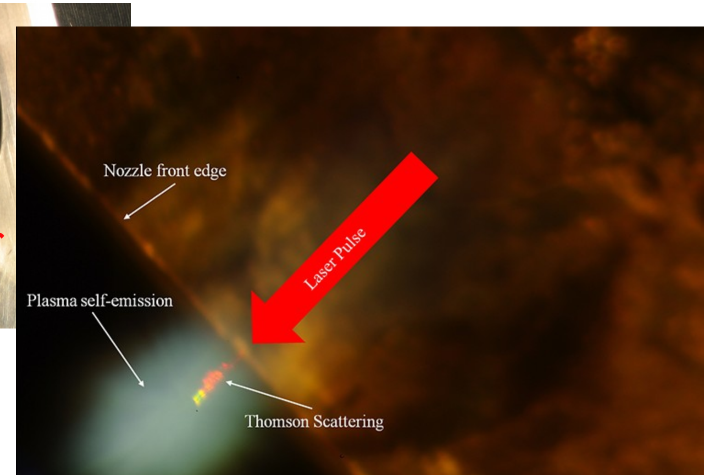
Basic arrangement

The laser pulse is focused in the proximity of the entrance edge of the gas-jet

Electrons are accelerated in the forward direction







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A taste of the LWFA "history"

1979: proposal by Tajima&Dawson

VOLUME 43, NUMBER 4 PHYSICAL REVIEW LETTERS 23 JULY 1979

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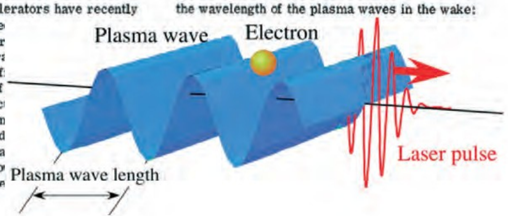
Collective plasma accelerators have recently received considerable the mental investigation. Ear lan[2] considered cosmic-ra tion by moving magnetic f netic waves.[2] In terms of tory technology for collec present-day electron bean of ~10^7 V/cm and power d On the other hand, the gla capable of delivering a po cm^2, and, as we shall see

the wavelength of the plasma waves in the wake:



2004: "Dream beam" front cover of Nature (3 papers reporting "high-quality" e$^-$ bunch production)

End of noughties: routine production of stable e$^-$ bunch

PRL **101**, 105002 (2008) PHYSICAL REVIEW LETTERS week ending 5 SEPTEMBER 2008

Intense γ-Ray Source in the Giant-Dipole-Resonance Range Driven by 10-TW Laser Pulses

A. Giulietti,[1,2] N. Bourgeois,[3] T. Ceccotti,[4] X. Davoine,[5] S. Dobosz,[4] P. D'Oliveira,[4] M. Galimberti,[1,*] J. Galy,[6] A. Gamucci,[1,2] D. Giulietti,[1,2,7] L. A. Gizzi,[1,2] D. J. Hamilton,[6,+] E. Lefebvre,[5] L. Labate,[1,2] J. R. Marquès,[3] P. Monot,[4] H. Popescu,[4] F. Réau,[4] G. Sarri,[1] P. Tomassini,[1,8] and P. Martin[4]
[1]*Intense Laser Irradiation Laboratory, IPCF, Consiglio Nazionale delle Ricerche, CNR Campus, Pisa, Italy*
[2]*INFN, Sezione di Pisa, Italy*
[3]*Laboratoire pour l'Utilisation des Lasers Intenses, CNRS UMR 7605, Ecole Polytechnique, Palaiseau, France*
[5]*Départeme*
[6]*Europ*

A γ-ray so absorption has 3D particle-in acceleration of the giant dipol gold sample, to electron-γ sou

DOI: 10.1103/P

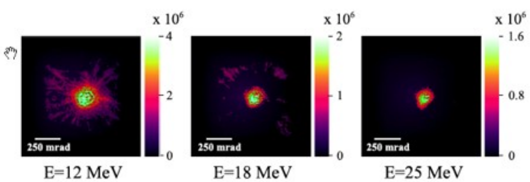


FIG. 1 (color online). Spatially resolved spectral data of the accelerated electrons from the SHEEBA detector.

2006: GeV energy reported

LETTERS

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nature physics | VOL 2 | OCTOBER 2006 | www.nature.com/naturephysics

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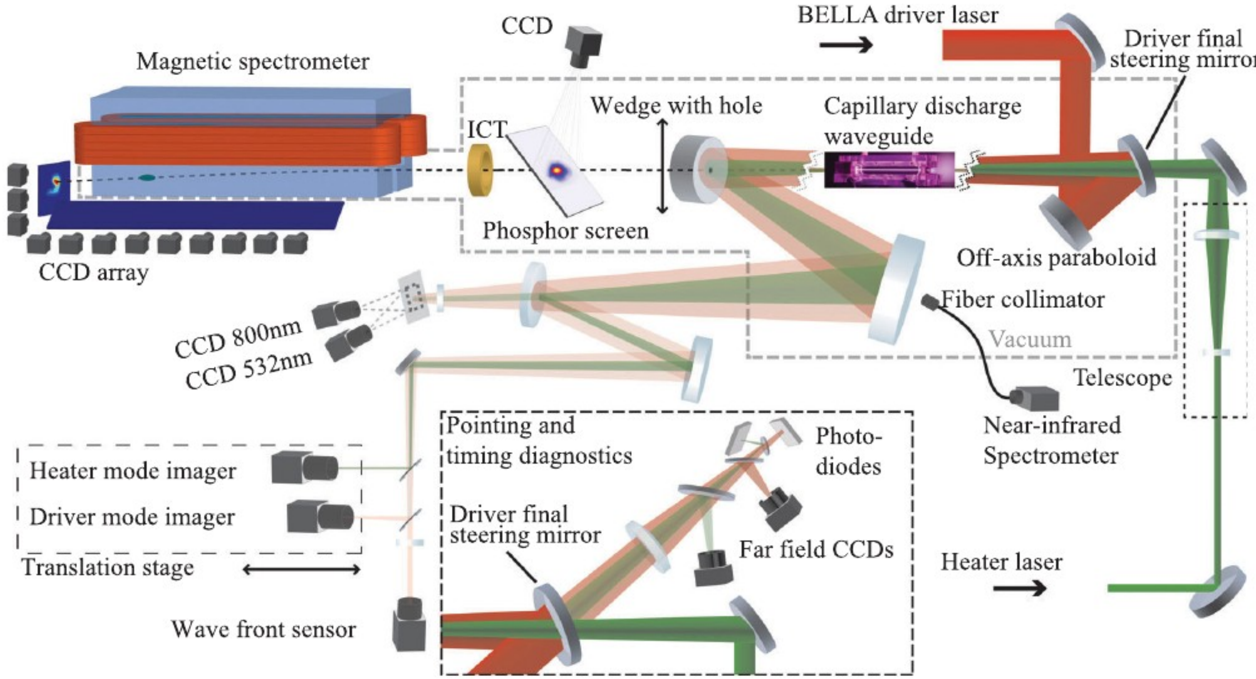
Current "record"

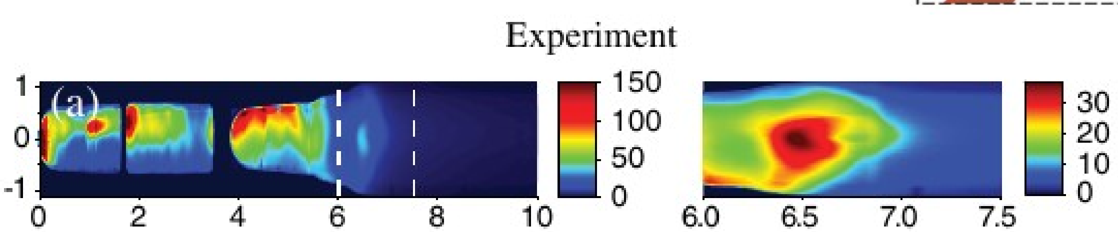
PHYSICAL REVIEW LETTERS **122,** 084801 (2019)

Editors' Suggestion **Featured in Physics**

Petawatt Laser Guiding and Electron Beam Acceleration to 8 GeV in a Laser-Heated Capillary Discharge Waveguide

A. J. Gonsalves,[1,*] K. Nakamura,[1] J. Daniels,[1] C. Benedetti,[1] C. Pieronek,[1,2] T. C. H. de Raadt,[1] S. Steinke,[1] J. H. Bin,[1]
S. S. Bulanov,[1] J. van Tilborg,[1] C
L. Fan-Chiang,[1,2] G. Bagdasarov,[3,4]





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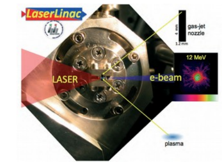
Past research on LWFA applications to medicine at the ILIL lab: "low-energy" e- bunches for Intra-Operatory RT

Comparison with "conventional" sources in medicine



Comparable figures as for electron energy, bunch charge, rep rate, average current

Bunch duration (→ peak current) of laser-driven accelerators much shorter → Much higher instantaneous dose rate

Parameter	LIAC (Sordina SpA)	Laser-LINAC
Max e^- kinetic energy	12 MeV	Up to 100s MeV
Total charge/bunch(shot)	1.8 nC	1 nC
Repetition rate	5-20 Hz	10 Hz
Average current	18 pA (@10Hz)	10 pA
Bunch duration	1.2 microseconds	~1 ps
Dose/pulse	0.5 – 5 cGy	Up to cGy?
Instantaneous dose rate	~10^7 Gy/s	>~10^{12}-10^{13} Gy/s

High-current e^- bunches (with respect to those from RF LINACS): different radiobiological effects?
Novel applications/protocols in perspectives?

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A. Giulietti, Proc. SPIE 10239 (2017); L. Labate, Proc. SPIE 10239 (2017); L. Labate *et al.*, J. Phys. D 49, 274501 (2016)

Possible new phenomena/applications in radiotherapy?

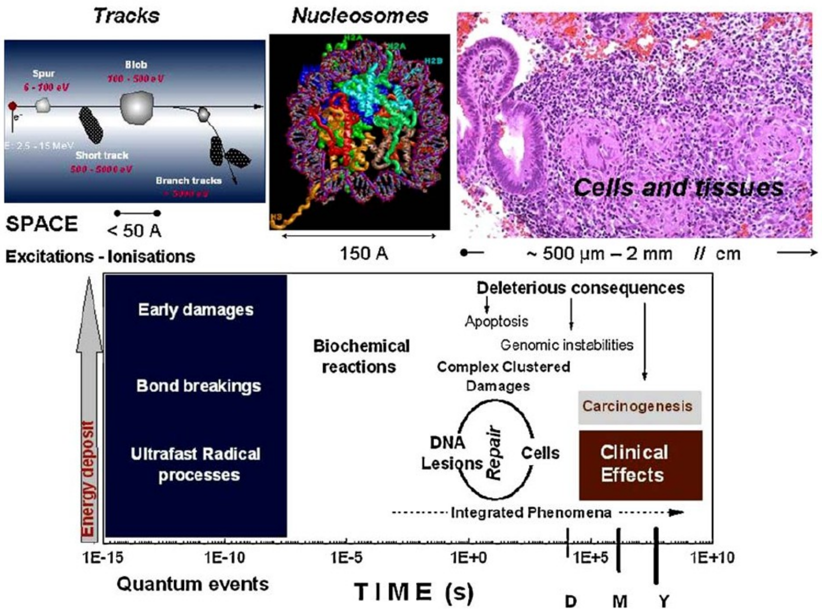
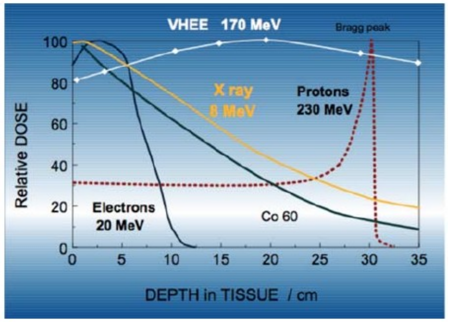


Figure credit: V. Malka *et al.*, Mut. Research **704**, 142 (2010)

Ultrafast radiation biology represents a newly emerging interdisciplinary field driven by the emerging of laser-driven particle accelerators

A challenge of ultrafast radiation biology is to approach directly the early electronic and radical processes inside confined clusters of ionization



MonteCarlo simulations show that the use of very high energy electron beams may lead to better dose delivery profiles in the case of deep tumors

250 MeV electrons *6 MeV photons* *difference*

Figure credit: T. Fuchs *et al.*, Phys. Med. Biol. **54**, 3315 (2009)

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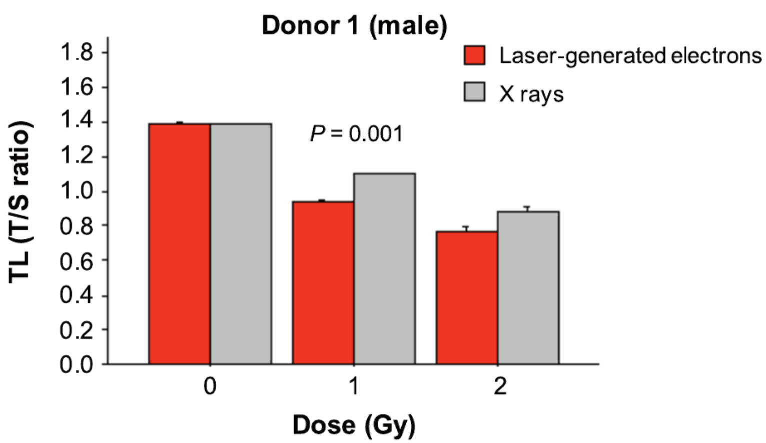
Past radiobiology experiments at ILIL with "low-energy" e- bunches: Comparative study of cell damage: radiation-induced telomere shortening

- Telomeres play a vitally important part in preserving the integrity and stability of chromosomes
- Telomere length was studied after irradiation with LWFA electron bunches and X-rays from an X-ray tube (standard in radiation biology)

Irradiations at different dose levels was carried out



Telomeres shorter than baseline from 0.1 Gy (p<0.001)

Results comparable for laser-driven electron bunches and X-rays

RADIATION RESEARCH **186**, 245–253 (2016)
0033-7587/16 $15.00

DOI: 10.1667/RR14266.1

Radiobiological Effectiveness of Ultrashort Laser-Driven Electron Bunches: Micronucleus Frequency, Telomere Shortening and Cell Viability

Maria Grazia Andreassi,[a,1] Andrea Borghini,[a] Silvia Pulignani,[a] Federica Baffigi,[b] Lorenzo Fulgentini,[b] Petra Koester,[b] Monica Cresci,[a] Cecilia Vecoli,[a] Debora Lamia,[c] Giorgio Russo,[c] Daniele Panetta,[a] Maria Tripodi,[a] Leonida A. Gizzi[b] and Luca Labate[b]

[a] *Genetics Unit, CNR Institute of Clinical Physiology, Pisa, Italy;* [b] *Intense Laser Irradiation Laboratory, CNR National Institute of Optics, Pisa, Italy; and* [c] *CNR Institute of Bioimaging and Molecular Physiology, Cefalù (PA), Italy*

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M.G. Andreassi *et al.*, Rad. Res. 186, 245 (2016)

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Motivations: laser-driven VHEE as a possible new tool for radiotherapy

Most common radiotherapy nowadays use *Bremsstrahlung* X-ray photon beams from MV clinical LINACs

This is historically due to the lack of availability of clinical VHEE LINAC sources

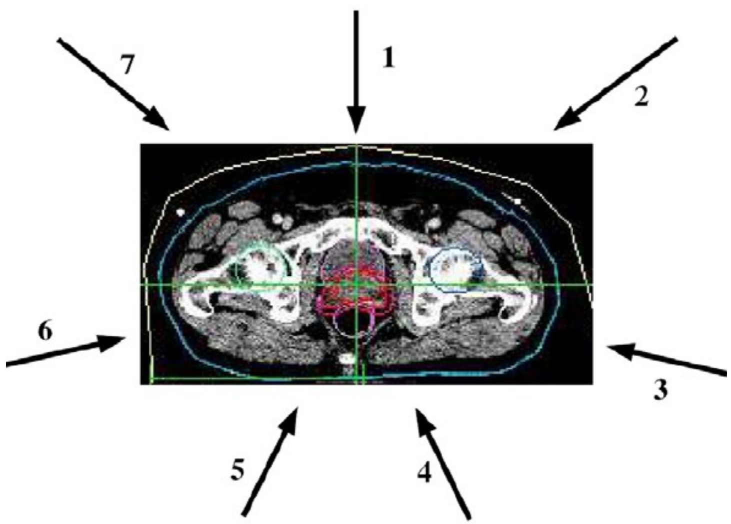
current limit of clinical LINACs: 22 MeV

→ unsuitable to treat deep-seated tumors, due to the steep attenuation profile in human tissues

Notable exception: Intra-Operatory Radiation Therapy (IORT) – 6-12 MeV

Bremsstrahlung photon beams: rather poor directionality, broad spectrum, long attenuation lengths in human tissues

→ "Advanced" X-ray modalities: Intensity-Modulated RadioTherapy (IMRT) coupled to Multi-Field irradiation



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Motivations: laser-driven VHEE as a possible new tool for radiotherapy (2)

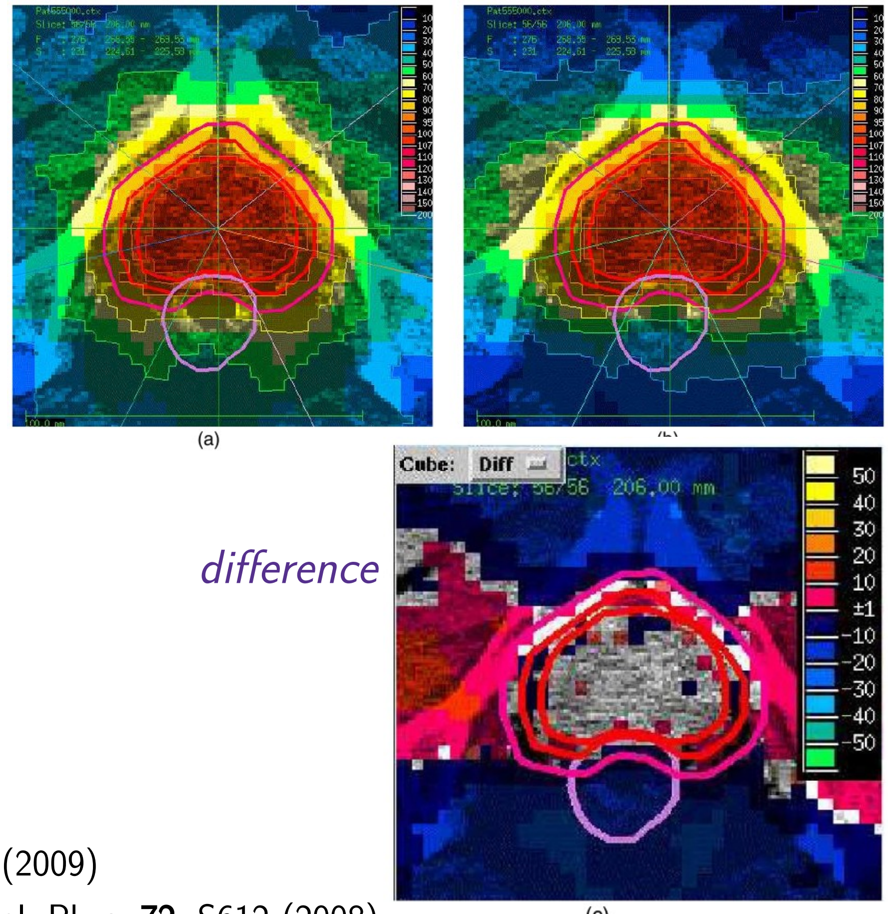
Laser-driven acceleration of electrons to >100MeV (up to ~250MeV) energy (so-called VHEE) have the potential to modify this scenario → revived interest for electron radiotherapy

Possible usage has been investigated over the past 10 years by means of Monte Carlo simulations, showing a potential for good dose conformation, comparable (or exceeding) that of current photon beam modalities

Quality of a prostate treatment plan evaluated for a 6MV IMRT and a VHEE treatment

- Better target coverage achieved
- Extent of the sparing of organs at risk found to be dependent on depth (due to e- exhibiting larger scattering)

6MV X-rays *150MeV e-* *difference*

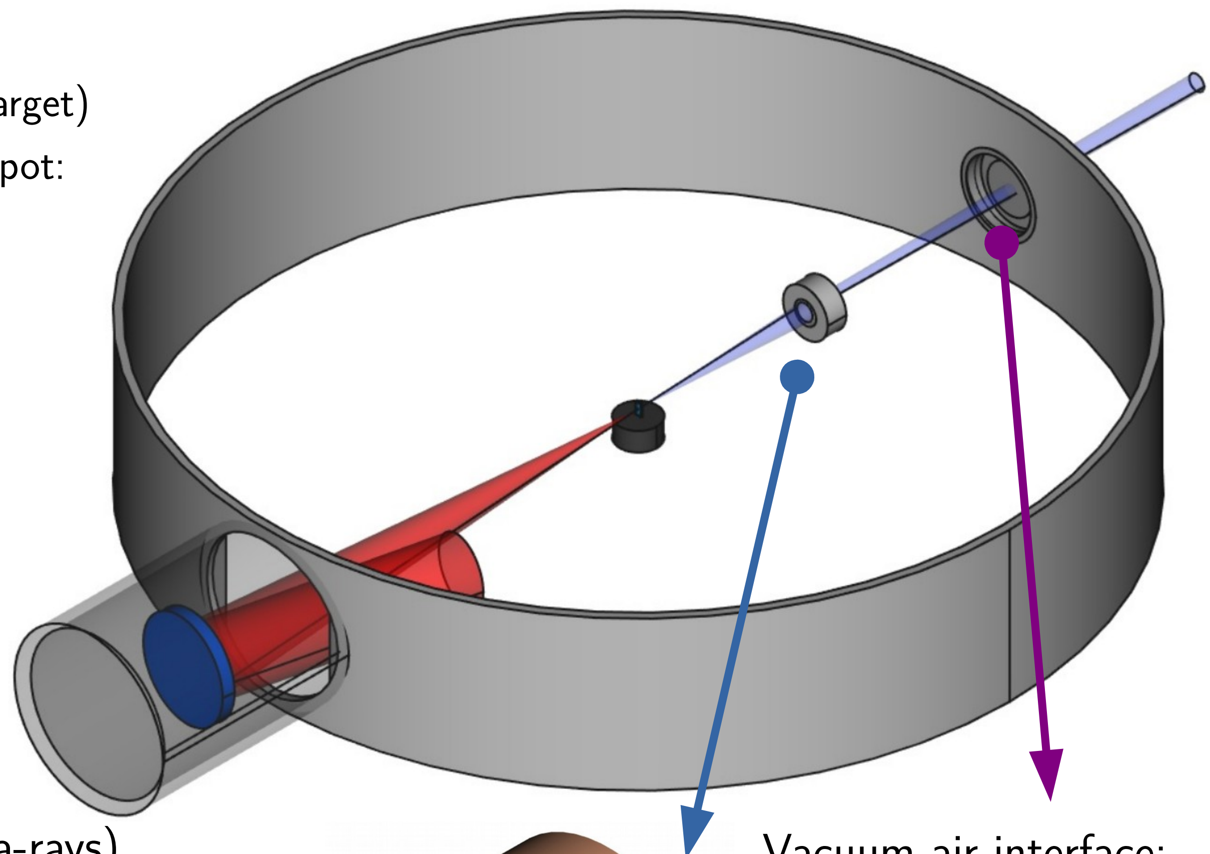


T. Fuchs *et al.*, Phys. Med. Biol. **54**, 3315 (2009)
Des Rosiers *et al.*, Int. J. Radiat. Oncol. Biol. Phys. **72**, S612 (2008)

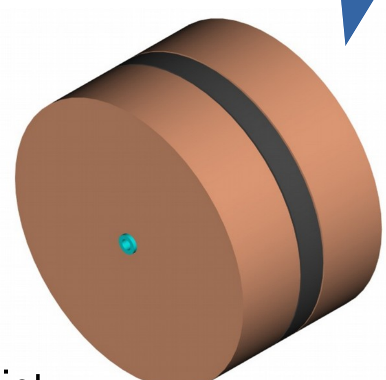
A quick look at the experiment setup/parameters

Laser beam figures

- 150TW beamline (>4J on target)
- beam energy in the central spot:
  <~ 3J (Strehl ratio ~0.7)
- focused with an f/~20 OAP
- w ~ 31micron
- a_0 ~ 1.7



e- bunch collimator
(minimize dose from gamma-rays)
- multi-layer PVC/Pb/PVC
- total thickness: 7cm
- teflon tube at the center,
  with a 2mm aperture
- placed 35cm downstream the gas-jet



Vacuum-air interface:
70micron thick kapton window

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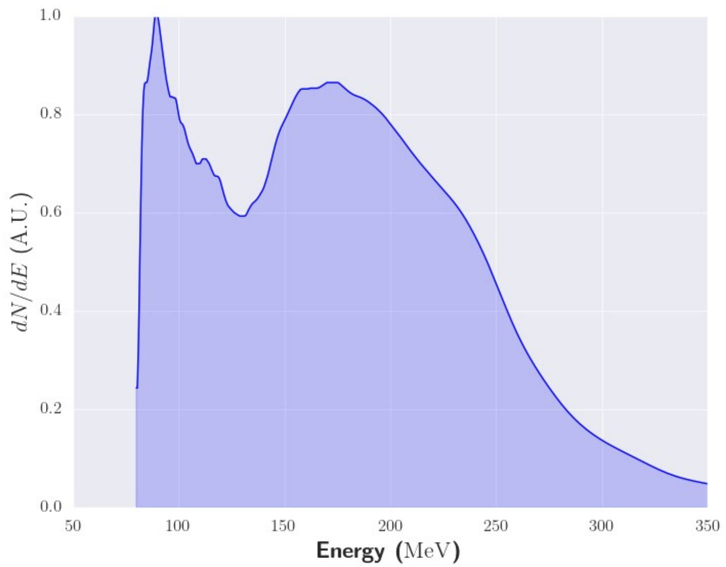
Electron spectra: main features

A LWFA condition delivering e- bunches with energy >~100MeV was seeked for (mainly by (de)tuning laser focus position, backing pressure and density profile)

Typical spectrum

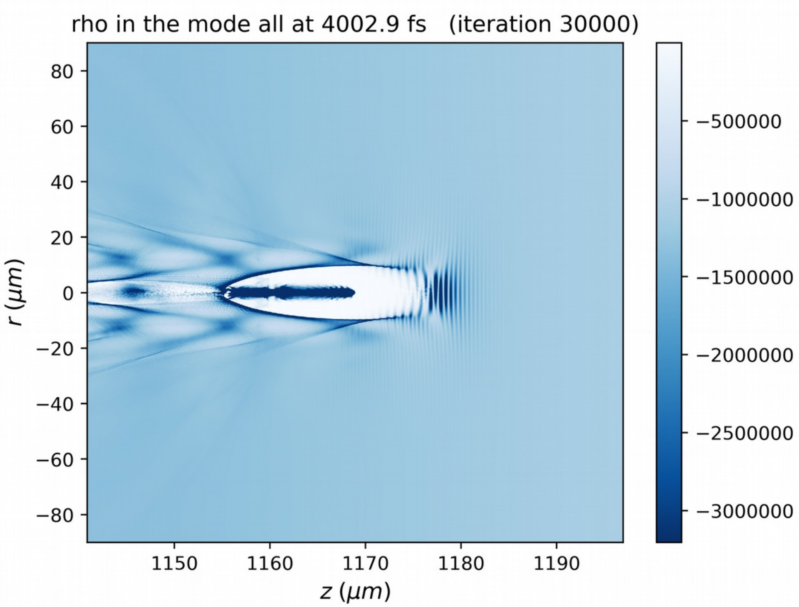


Most of the charge is contained in an energy interval 80-250 MeV

Average spectrum pretty stable when averaged over 20 shots

PIC simulations using the FBPIC code

- Cylindrical modes used: m= 0, 1
- $\Delta z = 0.05$ µm
- $\Delta r = 0.13$ µm
- 12 Macroparticles per cell
- ADK ionization ON
- Particle spline: linear



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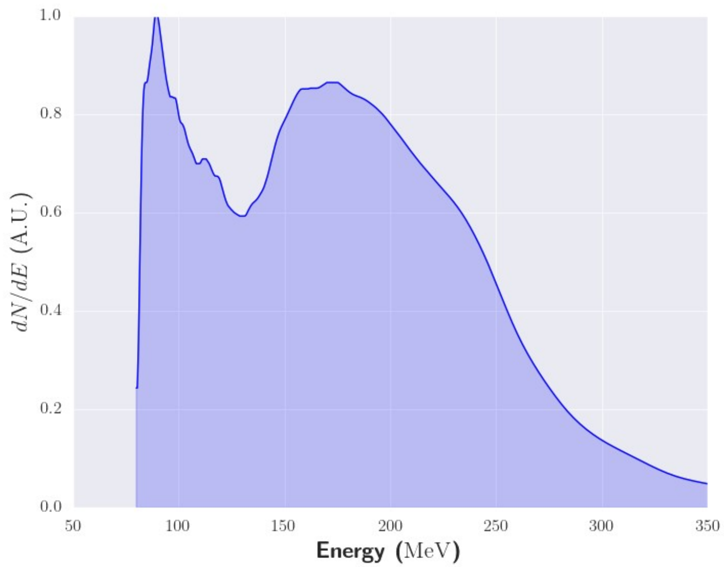
Electron spectra: main features

A LWFA condition delivering e- bunches with energy ~100MeV was seeked for (mainly by (de)tuning laser focus position, backing pressure and density profile)

Typical spectrum



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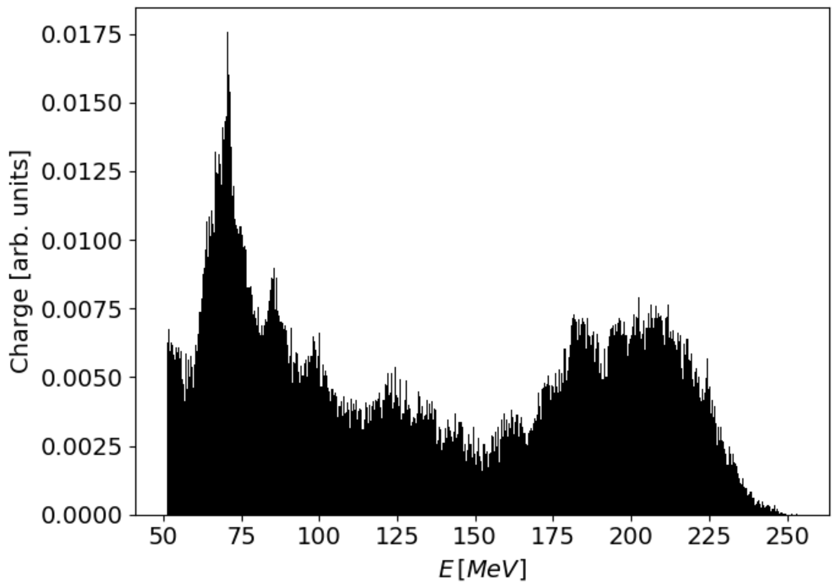

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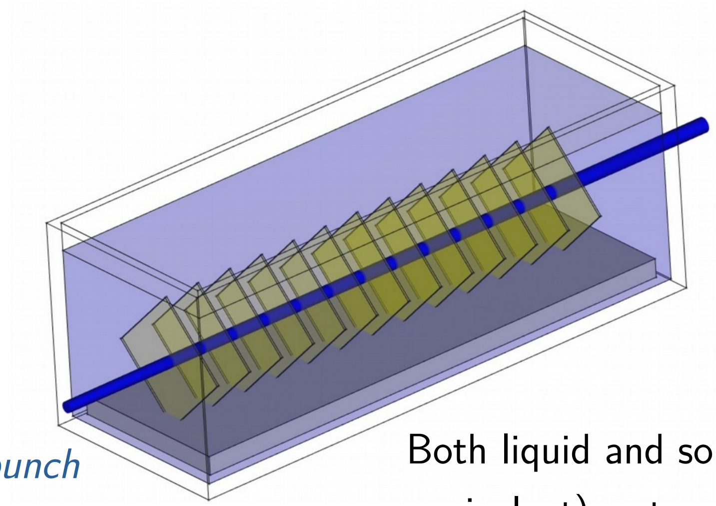
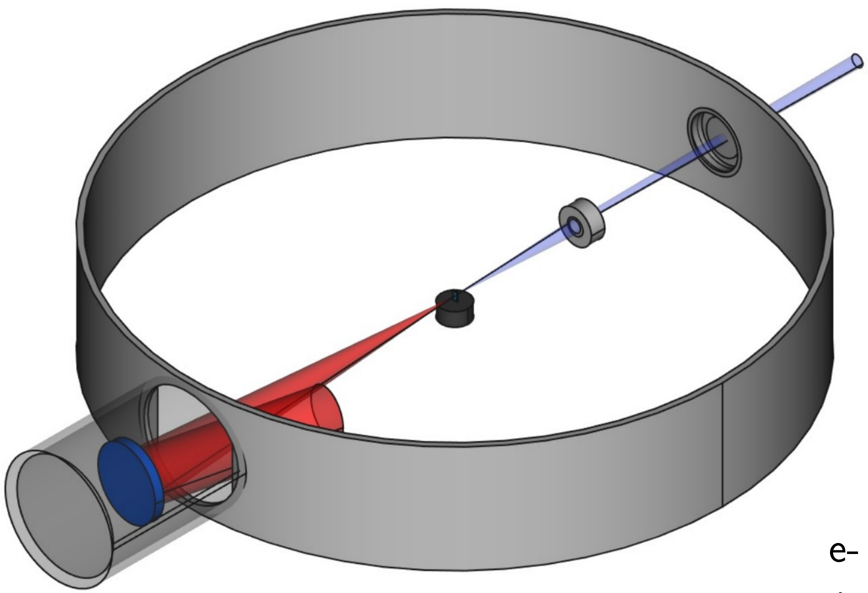
Beam dosimetry

Preliminary to applications relevant for effective RT protocols

"Intrinsic" (charge, divergence,...) beam properties studied w/o the collimator



Both liquid and solid (A150 tissue equivalent) water phantoms used



EBT3 Gafchromic films used as detector (showed* to exhibit energy independent response in the energy range of interest)

Precise calibration of each EBT3 batch carried out using 6MeV electron bunches from a conventional medical LINAC

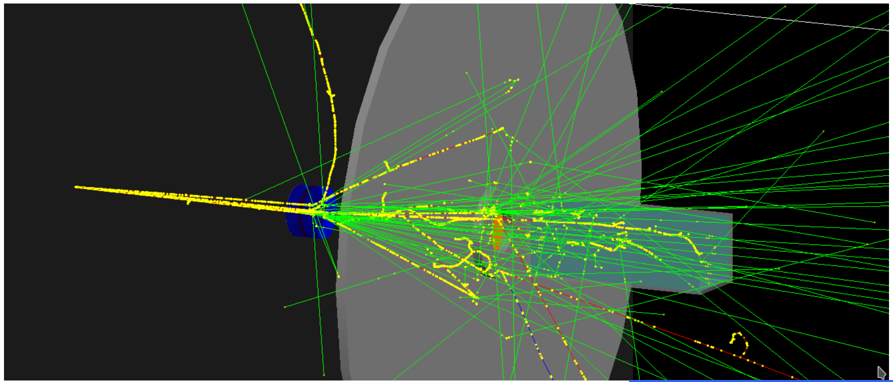
e- signal observed on Gaf films up to a depth of ~25cm (integrated over 100 laser shot)

CNR-INO

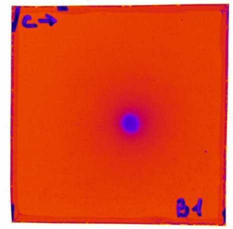
*A. Subiel *et al.*, Phys. Med. Biol. **59**, 5811 (2014)

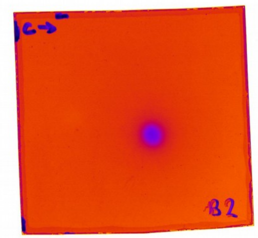
Beam dosimetry: comparison with Monte Carlo simulations

Monte Carlo simulations carried out using the GEANT4 toolkit

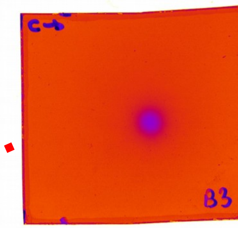


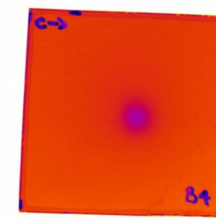
GEANT4 simulation tracking of few primary events

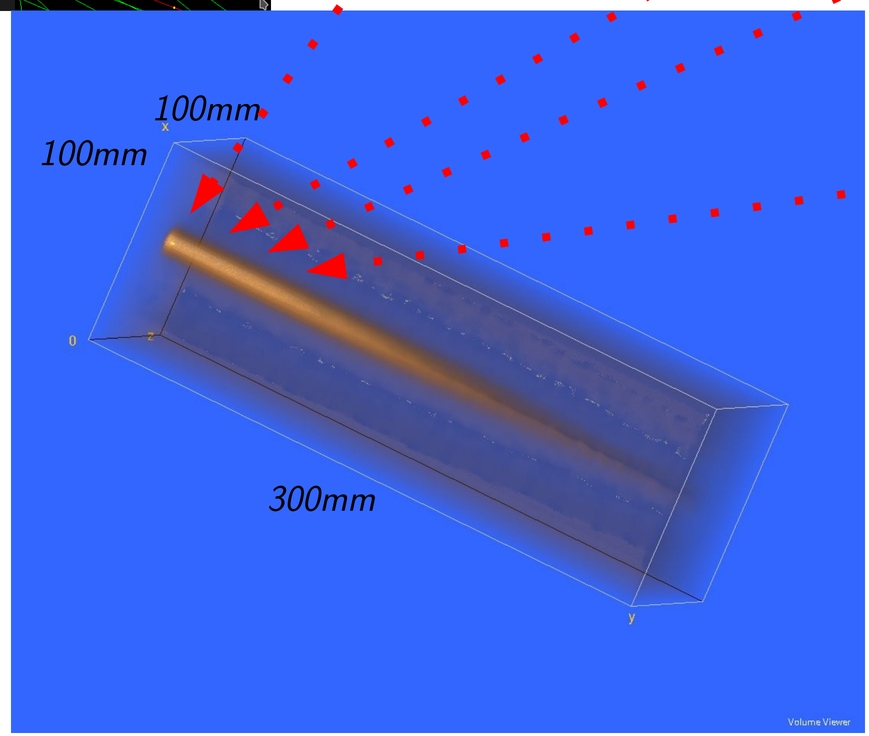




Gafchromic (scan) samples at different depths







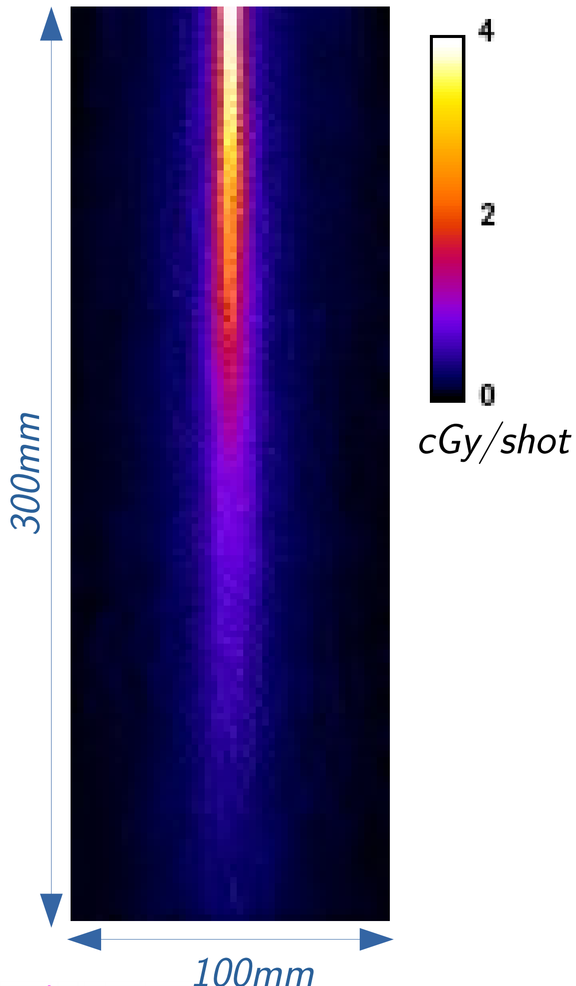
Rendering of the dose deposition pattern as provided by GEANT4 simulations

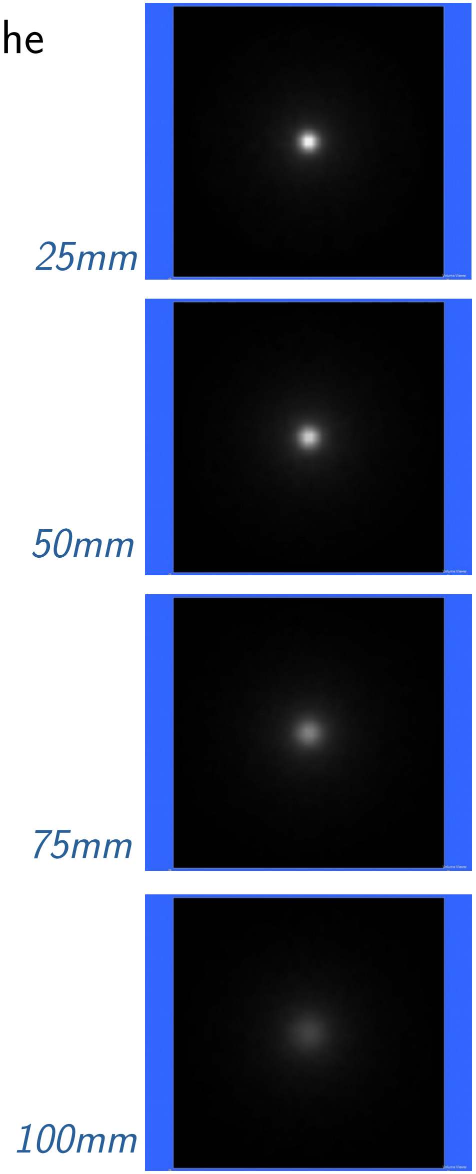
Size of the beam at the entrance ~3.5mm

Estimated bunch charge: ~10-20pC

Beam dosimetry: absolute dose and dose depth properties

Dose deposition pattern on the central (axis) plane





Dose/shot: 3-5 cGy (at z_{max})

Percentage Dose Depth:

z_{max} ~35mm

$R_{50\%}$ ~80-100mm

The dose deposition remains confined to few mm within ~150mm

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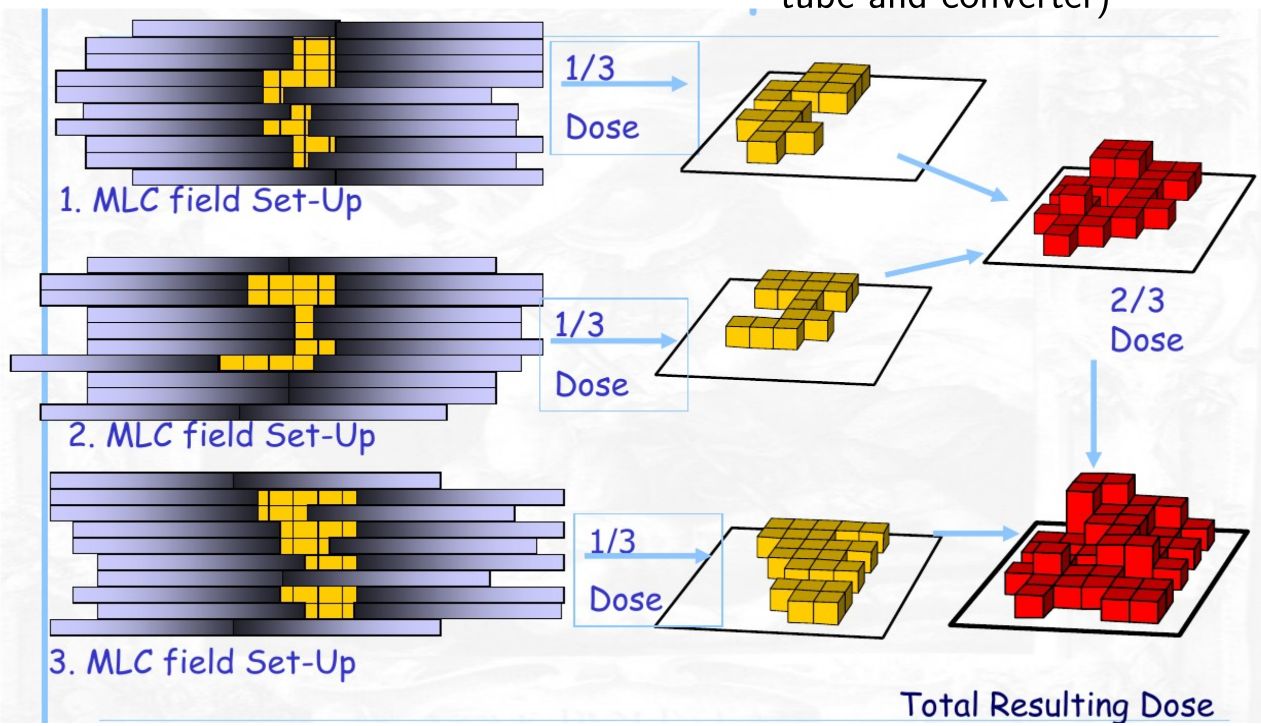
Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy is a method of radiation delivery allowing a fine shaped distribution of dose to avoid unsustainable damage to the tumor surrounding structures

It employs (photon) beamlets with 3-4mm size using a *Multi-Leaf Collimator* (a specialized, computer-controlled device made up by many tungsten *leaves* after the accelerator tube and converter)



Routinely delivered coupled to multi-field irradiation

Variants/improvements: VMAT (Volumetric Modulated Arc Therapy), ...

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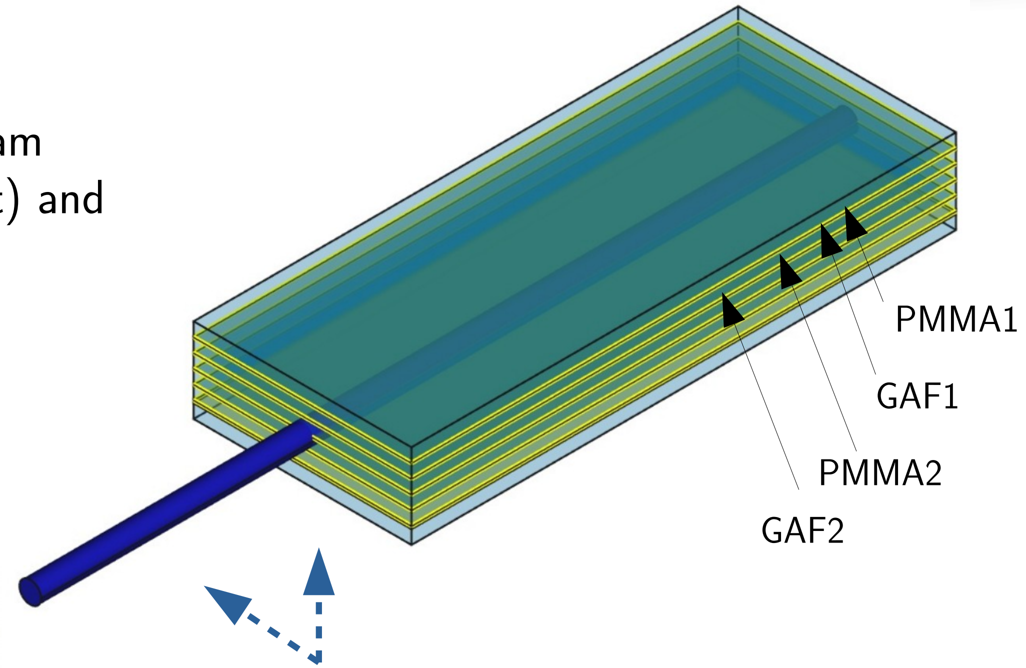
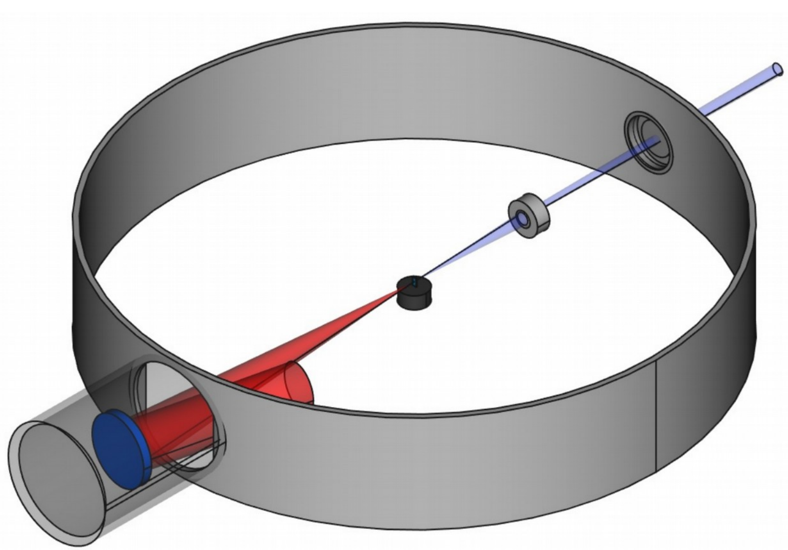
Our situation: “pencil (electron) beam”

IMRT can be obtained by changing the beam entrance point (2D pattern, at the moment) and varying the number of shots





PMMA phantom with Gafchromic films placed with surface parallel to the e- beam direction (“continuous” sampling along the longitudinal direction and one of the transverse direction, discrete sampling in the other transverse direction)

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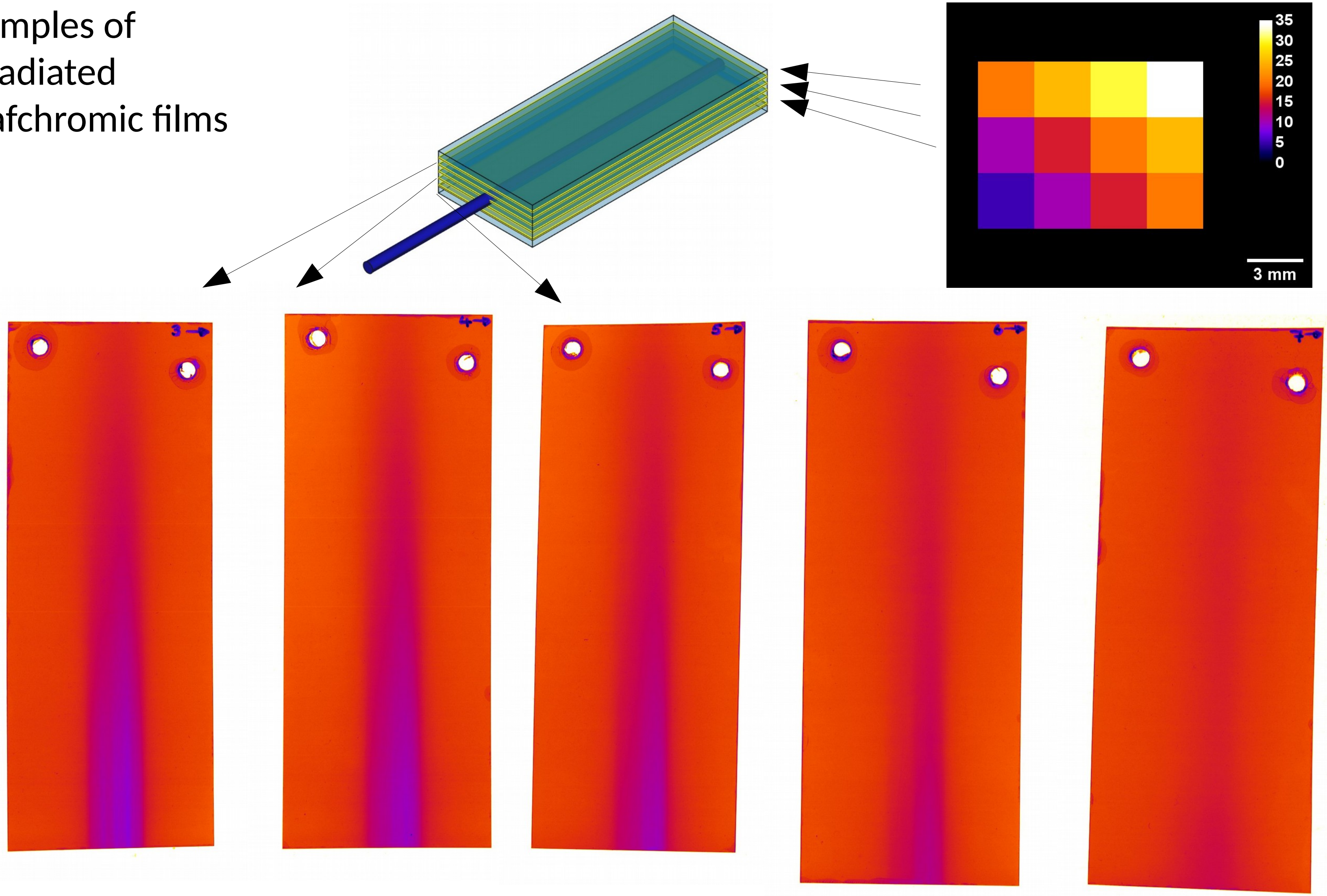
IMRT with laser-driven e- beams

Samples of irradiated Gafchromic films



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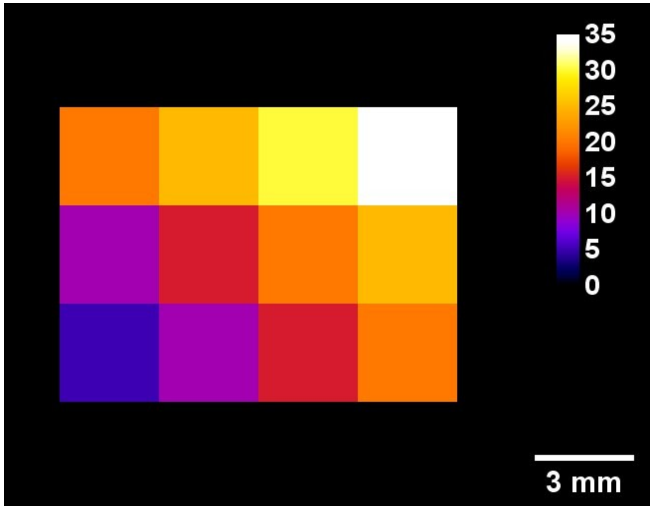
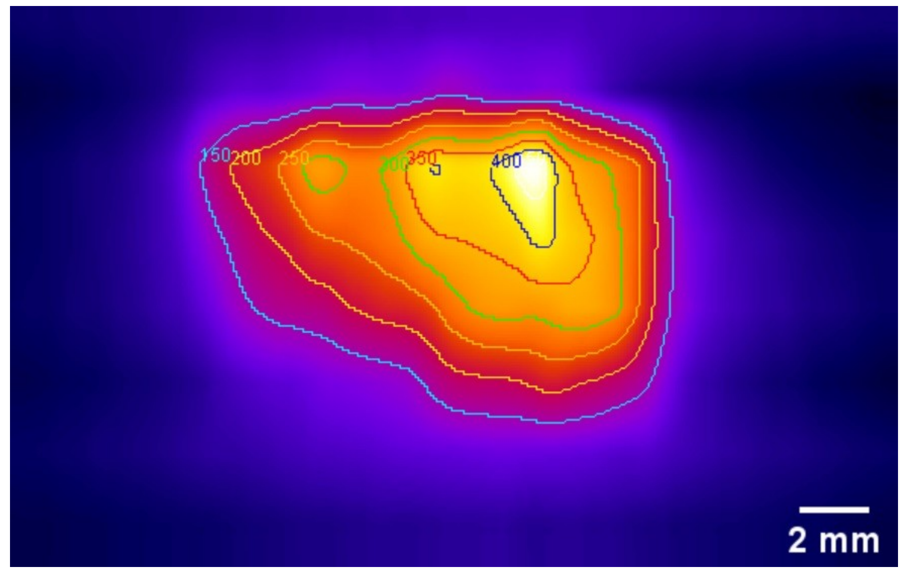
Mimicking a (single-field) IMRT: 2D modulation pattern

Irradiation pattern: (no. of shots on each position)



Experimental dose deposition transverse profile at z_{max}



Dose transverse profile tailoring with mm resolution

Comparison with expected pattern (as predicted by Monte Carlo simulations) still ongoing

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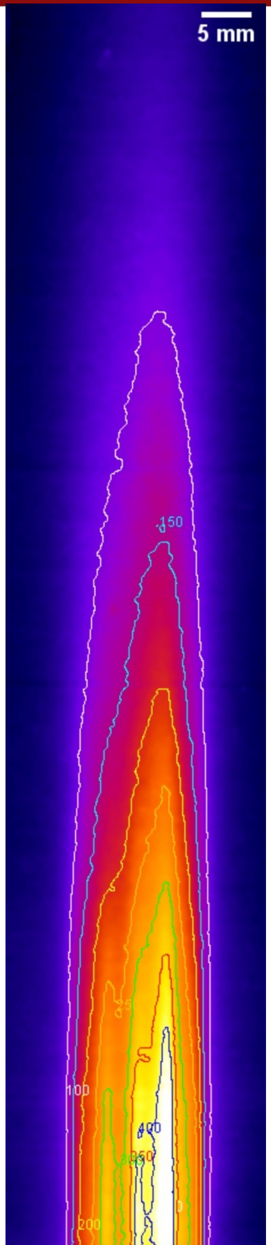
IMRT with laser-driven e- beams: depth dose delivery

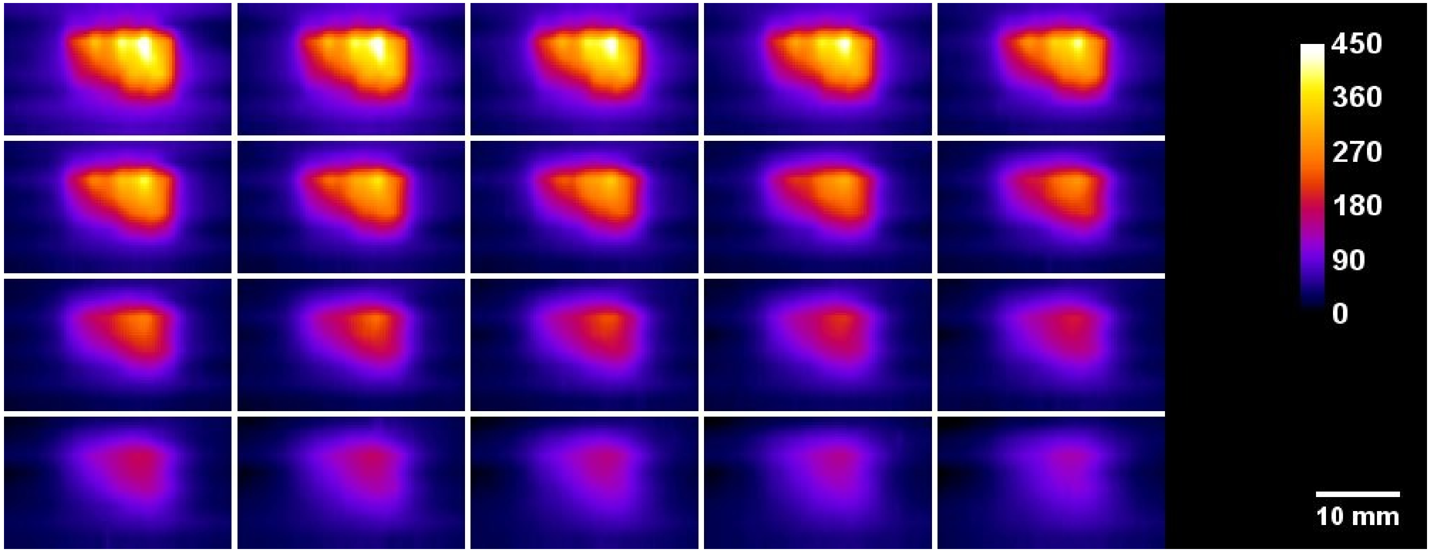
Isodose curves



200mm

400 cGy ---
350 cGy ---
300 cGy ---
250 cGy ---
200 cGy ---
150 cGy ---
100 cGy ---

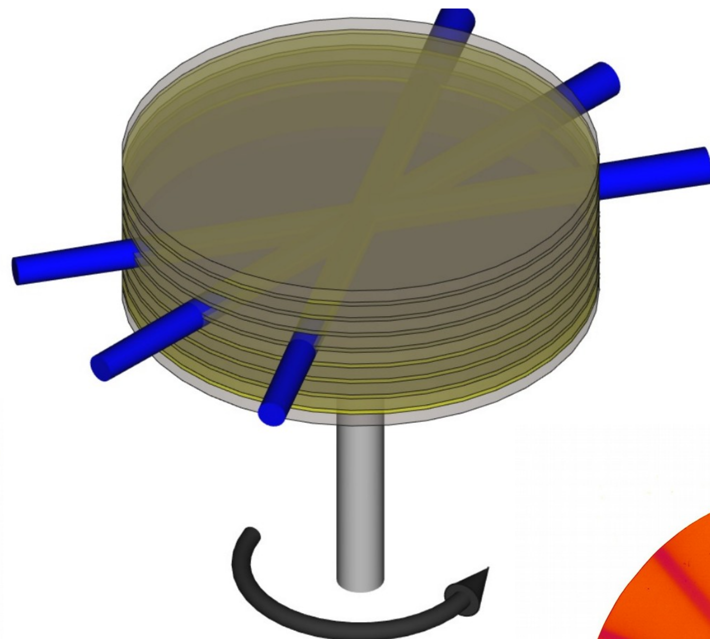
Transverse dose maps at different depths

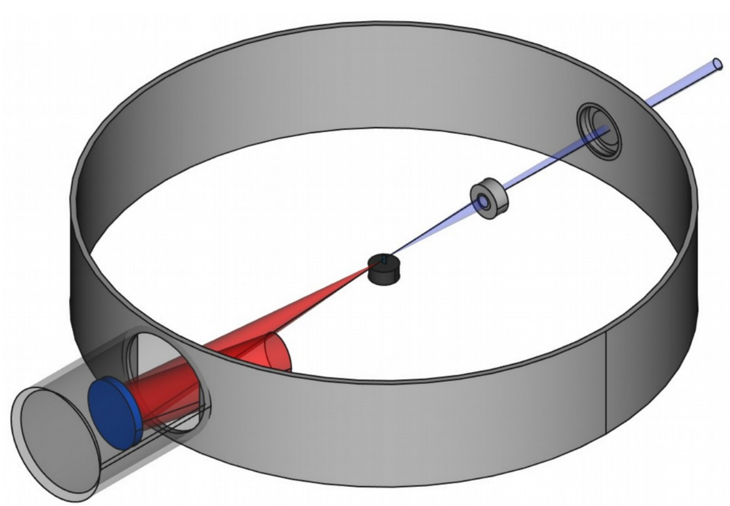


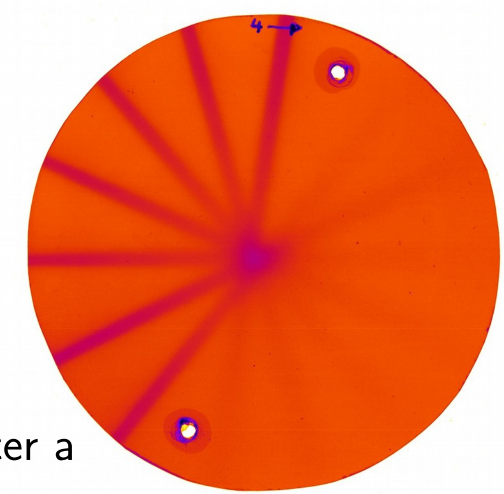
Transverse dose deposition pattern retains its (given) pattern within <1mm along the whole depth – good direction stability

Multifield irradiation: the experimental scheme

PMMA cylindrical phantom, made up by thin cylinders interleaved with round Gaf films







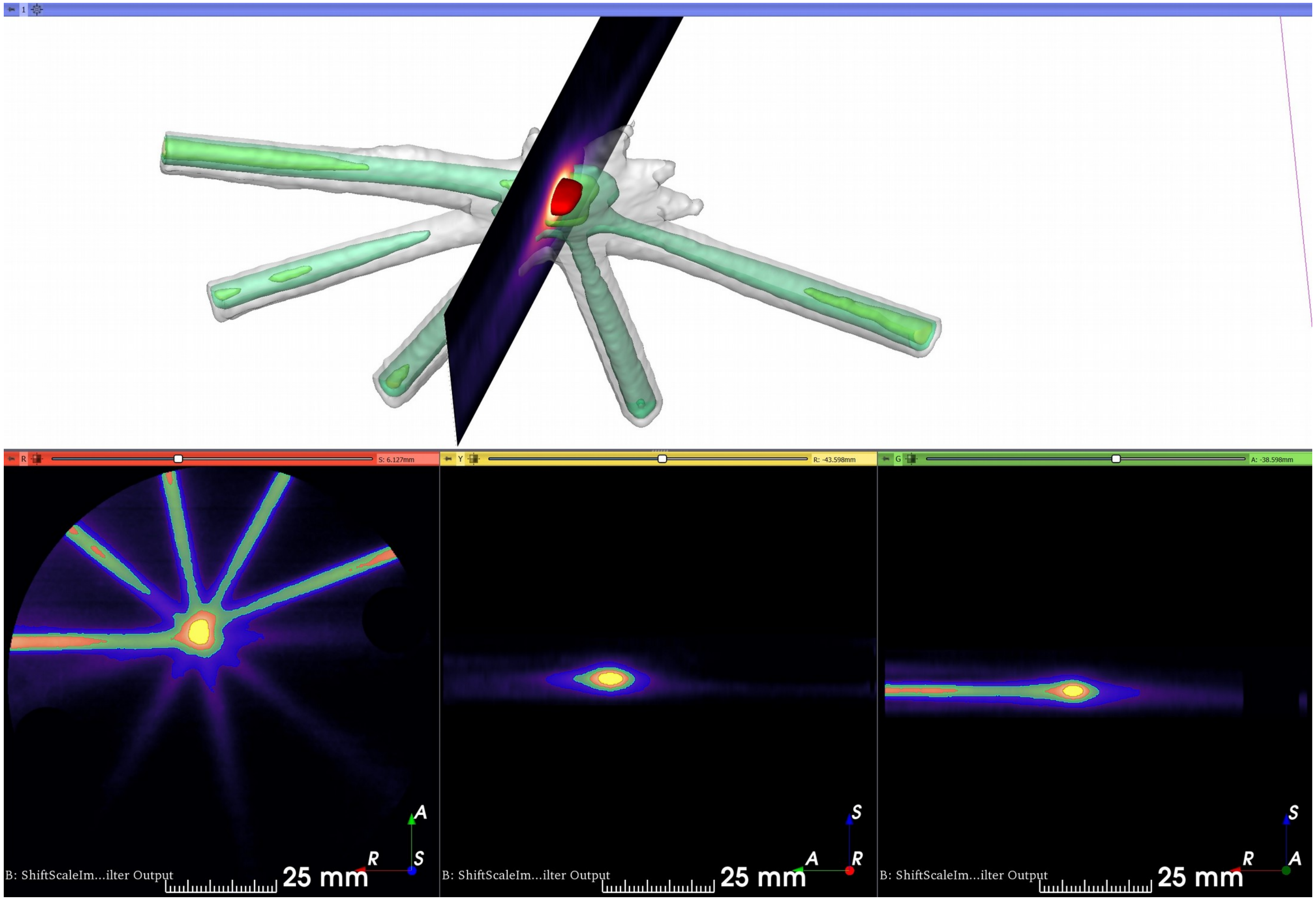
Example of irradiated Gaf after a 7 field (7 angles) irradiation

Multifield irradiation: 5-fields results

First irradiation scheme: 5 fields (at 40degree to each other), each irradiated with 40 laser shots

Up to ~2.5Gy reached on a small volume (~5mm size) at the (rotation) center

<20cGy distributed over a volume with ~15-20mm typical size surrounding this volume



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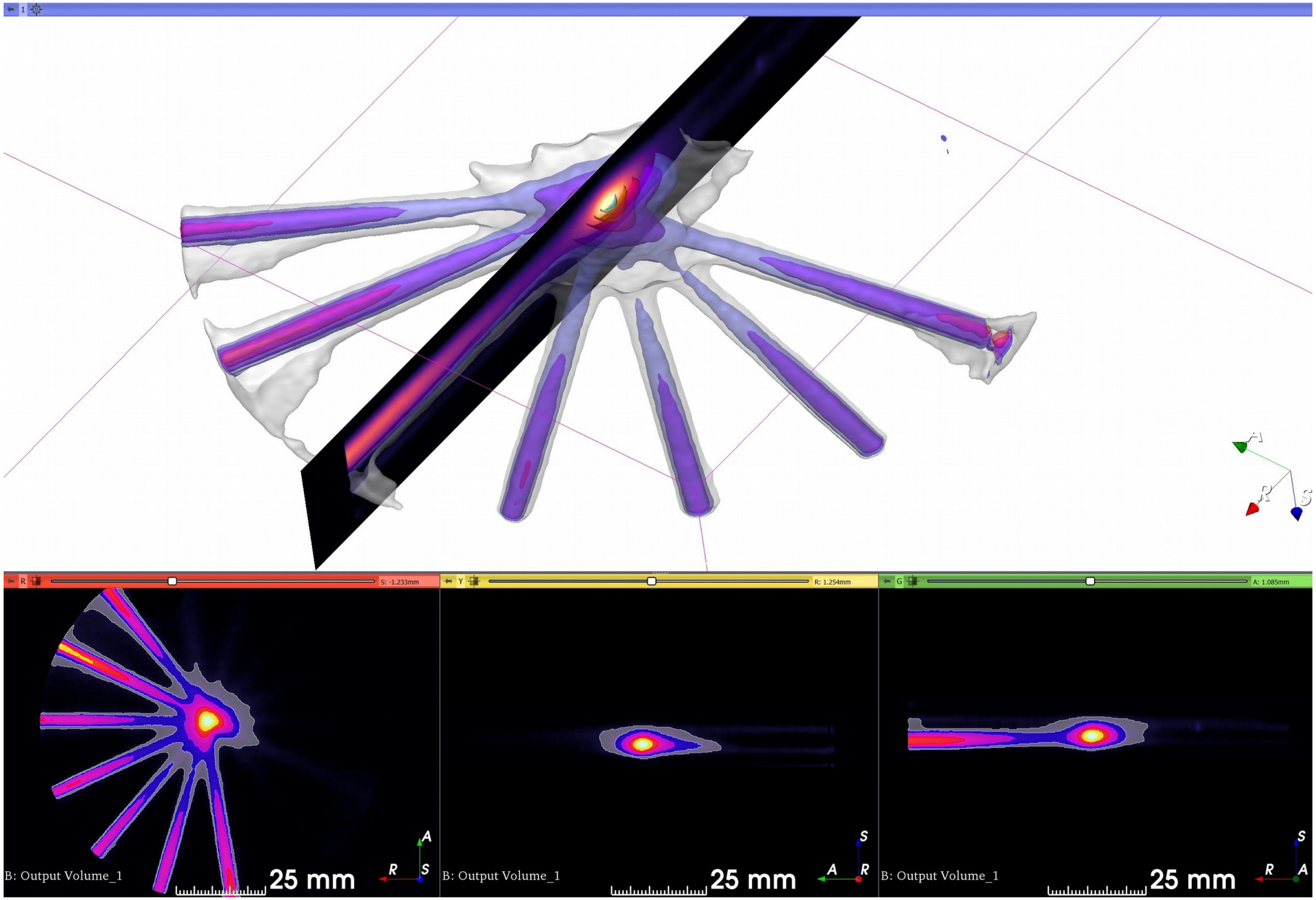
Multifield irradiation: 7-fields results

Improved irradiation scheme: 7 fields (at 25degree to each other), each irradiated with 30 laser shots



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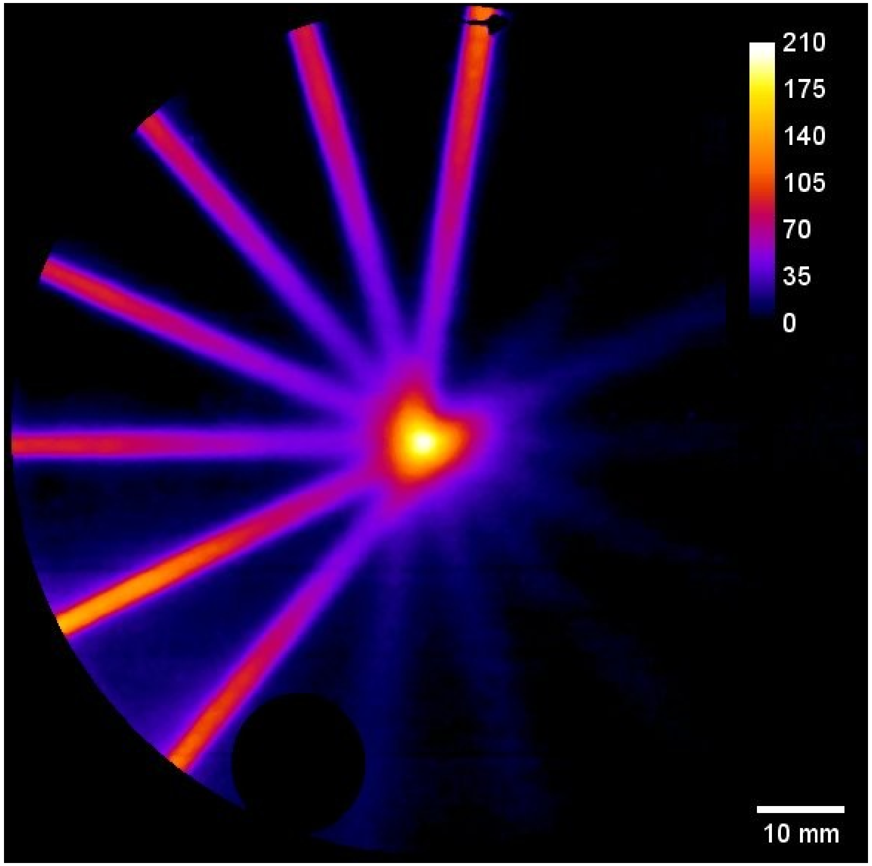
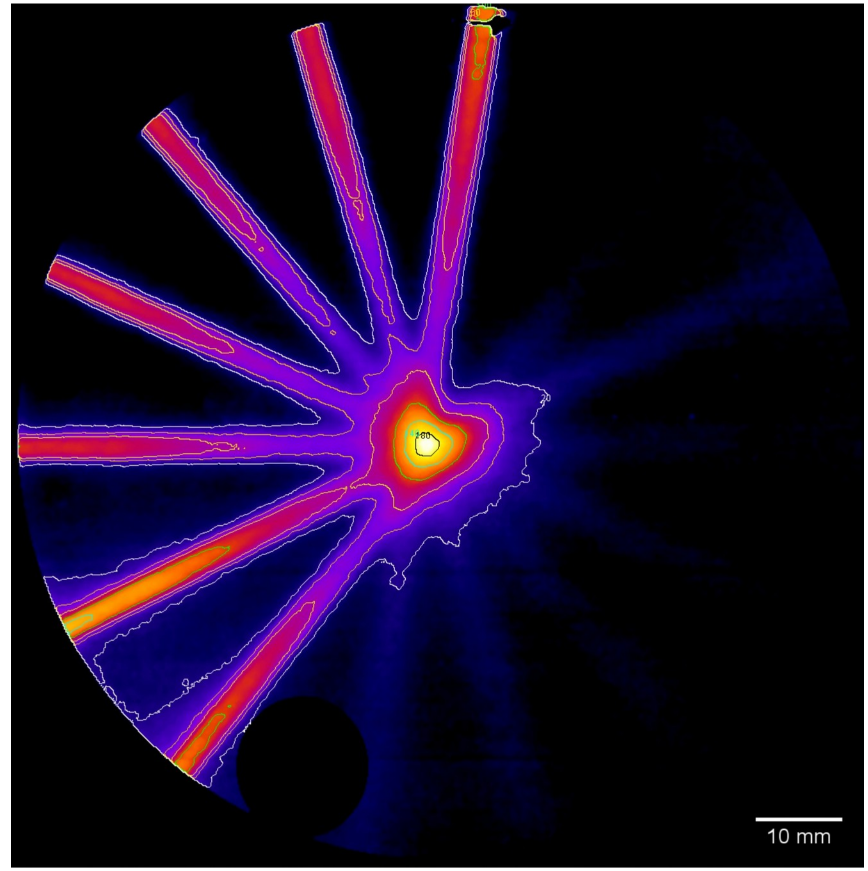
Multifield irradiation: 7-fields results



Isodose curves on a longitudinal plane



20 cGy ---	40 cGy ---
60 cGy ---	100 cGy ---
140 cGy ---	180 cGy ---

Improved dose deposition localization

Not negligible (accumulated) dose fluctuations (~20%) between different fields (i.e., shot series)

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FLASH-RT with laser-driven VHEE?

Cite this article as:
Durante M, Bräuer-Krisch E, Hill M. Faster and safer? FLASH ultra-high dose rate in radiotherapy. *Br J Radiol* 2018; **91**: 20170628.

COMMENTARY

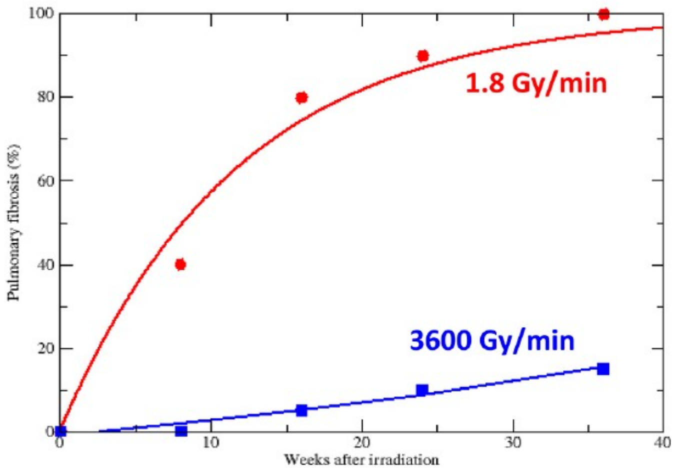
Faster and safer? FLASH ultra-high dose rate in radiotherapy

[1]MARCO DURANTE, PhD, [2]ELKE BRÄUER-KRISCH, PhD and [3]MARK HILL, PhD

ABSTRACT

Recent results from the Franco-Swiss team of Institute Curie and Centre Hospitalier Universitaire Vaudois demonstrate a remarkable sparing of normal tissue after irradiation at ultra-high dose rate (>40 Gy s^{-1}). The "FLASH" radiotherapy maintains tumour control level, suggesting that ultra-high dose rate can substantially enhance the therapeutic window in radiotherapy. The results have been obtained so far only with 4–6 MeV electrons in lung and brain mouse model. Nevertheless, they have attracted a great attention for the potential clinical applications. Oxygen depletion had been discussed many years ago as a possible mechanism for reduction of the damage after exposure to ultra-high dose rate. However, the mechanism underlying the effect observed in the FLASH radiotherapy remains to be elucidated.

Figure 1. Time dependence of pulmonary fibrosis in C57BL/6J mice after thoracic irradiation at conventional (circles) or ultra-high dose rate (squares). Data points and all details in reference Favaudon et al[1] lines are guides for the eye.



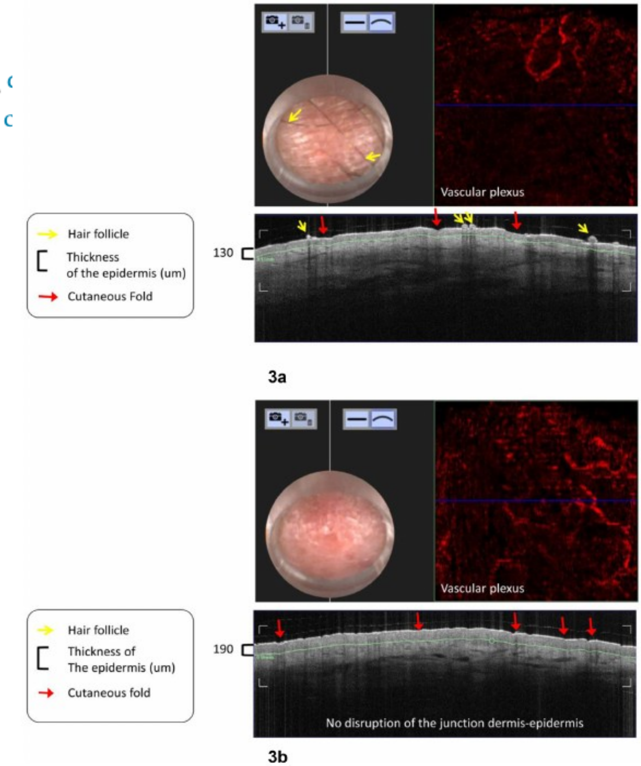
FLASH-RT with laser-driven VHEE?

Radiotherapy and Oncology 139 (2019) 18–22

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [c]
Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c]

Material & methods: A 75-year-old patient presented with a multiresistant CD30+ T-cell cutaneous lymphoma disseminated throughout the whole skin surface. Localized skin RT has been previously used over 110 times for various ulcerative and/or painful cutaneous lesions progressing despite systemic treatments. However, the tolerance of these RT was generally poor, and it was hypothesized that FLASH-RT could offer an equivalent tumor control probability, while being less toxic for the skin. This treatment was given to a 3.5-cm diameter skin tumor with a 5.6-MeV linac specifically designed for FLASH-RT.



could offer an equivalent tumor control probability, while being less toxic for the skin. This treatment was given to a 3.5-cm diameter skin tumor with a 5.6-MeV linac specifically designed for FLASH-RT. The prescribed dose to the PTV was 15 Gy, in 90 ms. Redundant dosimetric measurements were per-

FLASH-RT with (laser-driven) VHEE

Cite this article as:
Durante M, Bräuer-Krisch E, Hill M. Faster and safer? FLASH ultra-high dose rate in radiotherapy. *Br J Radiol* 2018; **91**: 20170628.

COMMENTARY

Faster and safer? FLASH ultra-high dose rate in radiotherapy

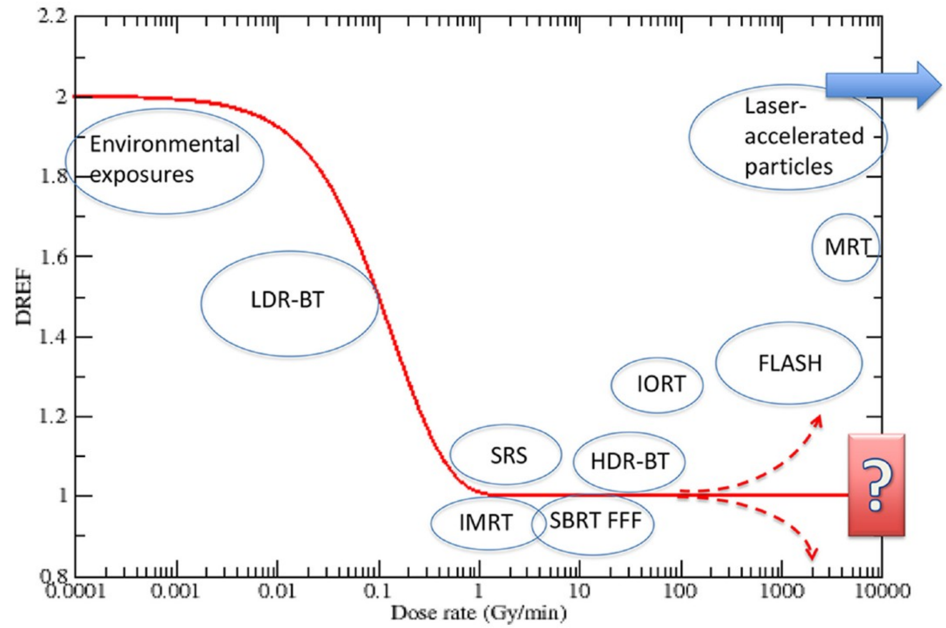
[1]MARCO DURANTE, PhD, [2]ELKE BRÄUER-KRISCH, PhD and [3]MARK HILL, PhD

Electron bunches offer a faster way to ultra-high dose rate RT (due to efficiency considerations)

Laser-driven VHEE offer a way to FLASH RT of deep tumors

→ But need laser development to increase the average power

Figure 2. DREF as a function of the dose rate. Different exposure scenarios at different dose-rate levels are shown in the circles. DREF, dose-rate effectiveness factor; HDR-BT, high dose-rate brachytherapy; IMRT, intensity modulated radiotherapy; IORT, intraoperatory radiotherapy; LDR-BT, low dose-rate brachytherapy; MRT, microbeam radiotherapy; SBRT-FFF, stereotactic body radiotherapy flattening filter free; SRS, stereotactic radiosurgery.



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Contents

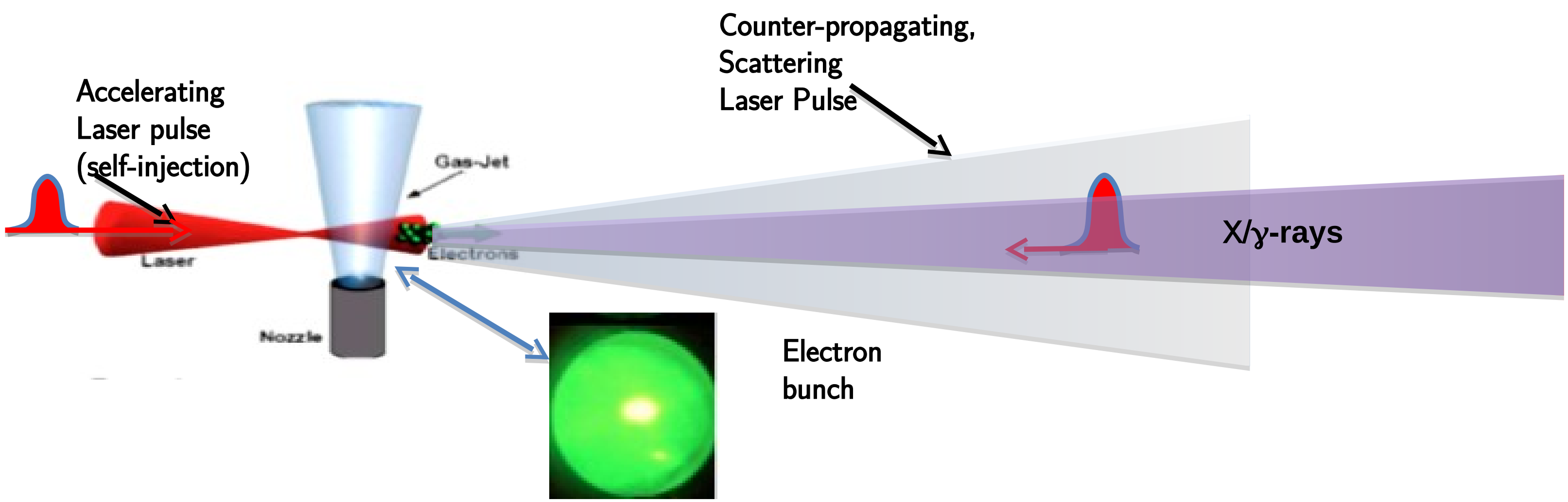
- A very short introduction to laser-driven electron acceleration
- Electron acceleration experiments for direct e-beams applications in medicine (radiotherapy)
  - Low-energy beams: Intra-Operatory Radiation Therapy (IORT)
  - Very-High Energy Electrons (VHEE):

    Motivations: Laser-driven VHEE sufficiently mature to possibly open up new frontiers in radiotherapy protocols

    Preliminary steps toward "real" biomedical applications: Demonstration of Intensity Modulation and Multiple-Field irradiation
- **All-optical advanced X-ray sources: a compact platform for 4D microCT of small animals**
- Summary and conclusions

All-optical Thomson Scattering X-ray sources

An all-optical X/γ-ray source basically takes advantage of the extreme compactness of a LWFA accelerator to enable "**table-top**" X/γ-ray sources to be developed, based on a secondary process (Thomson Scattering, betatron, *Bremsstrahlung)* from the e-bunch



PRL 110, 155003 (2013) PHYSICAL REVIEW LETTERS week ending 12 APRIL 2013

MeV-Energy X Rays from Inverse Compton Scattering with Laser-Wakefield Accelerated Electrons

S. Chen,[1] N. D. Powers,[1] I. Ghebregziabher,[1] C. M. Maharjan,[1] C. Liu,[1] G. Golovin,[1] S. Banerjee,[1] J. Zhang,[1] N. Cunningham,[1,*] A. Moorti,[1,†] S. Clarke,[2] S. Pozzi,[2] and D. P. Umstadter[1,‡]

[1]*Department of Physics and Astronomy, University of Nebraska, Lincoln, Nebraska 68588, USA*
[2]*Department of Nuclear Engineering and Radiological Sciences, University of Michigan, Ann Arbor, Michigan 48109, USA*
(Received 21 November 2012; published 10 April 2013)

We report the generation of MeV x rays using an undulator and accelerator that are both driven by the same 100-terawatt laser system. The laser pulse driving the accelerator and the scattering laser pulse are independently optimized to generate a high energy electron beam (> 200 MeV) and maximize the output x-ray brightness. The total x-ray photon number was measured to be $\sim 1 \times 10^7$, the source size was 5 μm, and the beam divergence angle was ~10 mrad. The x-ray photon energy, peaked at 1 MeV (reaching up to 4 MeV), exceeds the thresholds of fundamental nuclear processes (e.g., pair production and photodisintegration).

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Pioneering experiments on TS sources with laser-driven electron bunches

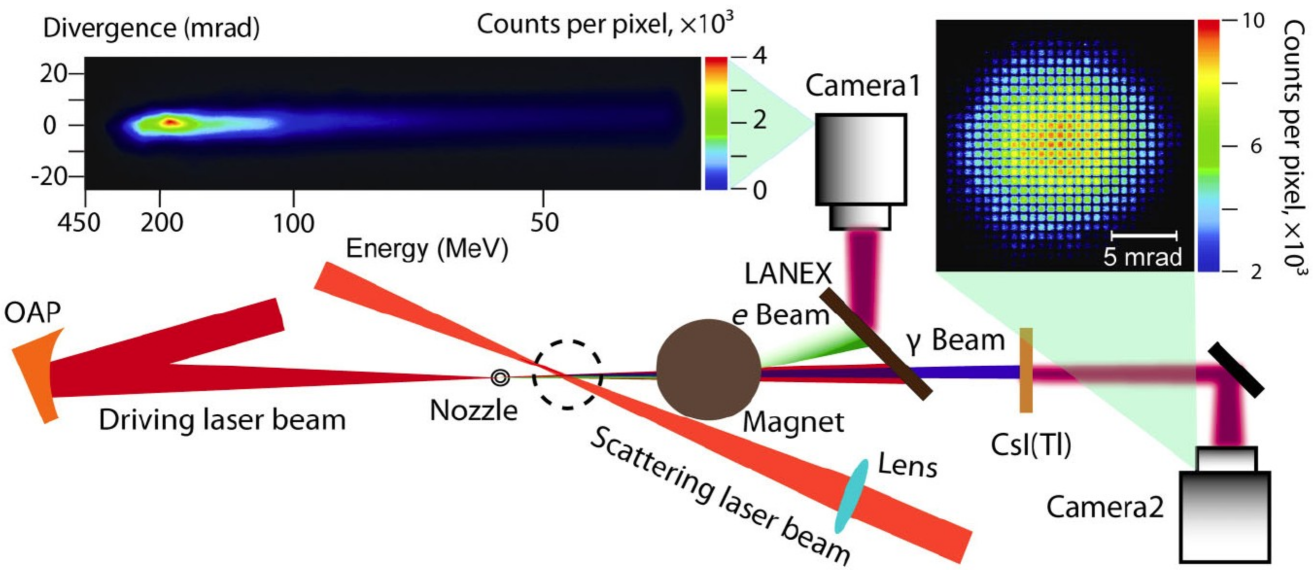
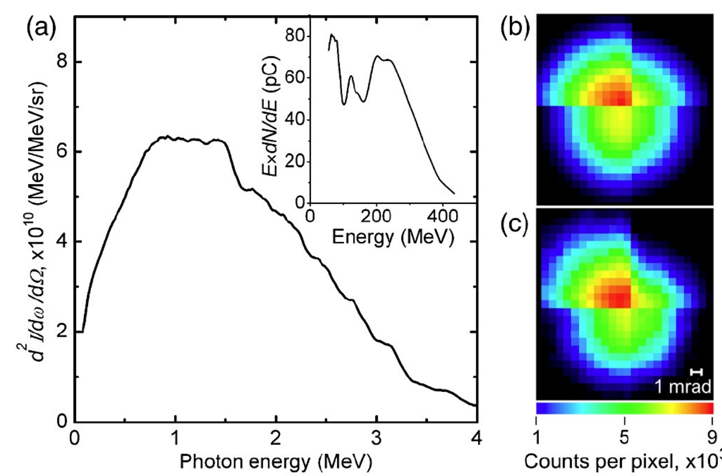


TABLE I. Typical experimental parameters for scattering laser (ω_0), electron (e), and gamma (γ) beams.

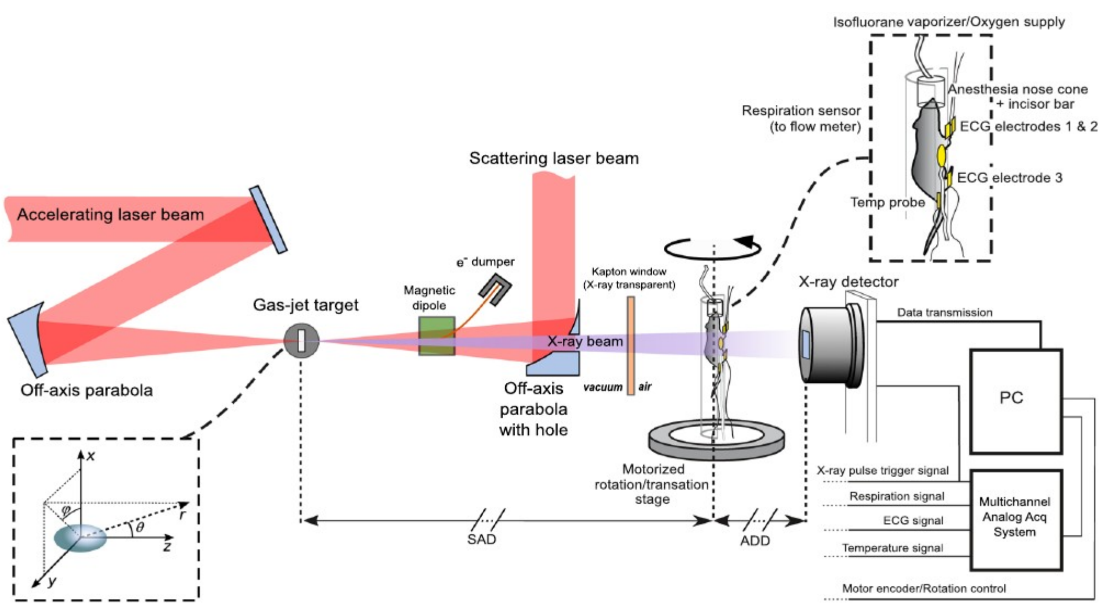
Beam	Parameter	Symbol	Value
ω_0	Energy	E_{laser}	0.5 J/pulse
	Wavelength	λ	800 nm
	Pulse duration	τ_s	90 fs (FWHM)
	Spot size	σ_L	9 ± 1 μm (rms)
	Number of laser oscillations/pulse	N_{laser}	34
	Average power	P_L	5.6 TW
	Normalized field strength	a_0	0.4
	Photon energy	E_L	1.5 eV
	Interaction angle	Φ	170 deg
e	Source size	σ_e	6 ± 3 μm (rms)
	Cutoff energy[a]	E_c	250 MeV
	Divergence[b]	θ_e	5 mrad (FWHM)
	Total charge	Q	120 pC
γ	Source size	σ_γ	5 ± 3 μm (rms)
	Divergence	θ_γ	12.7 mrad (FWHM)
	Peak energy	E_γ	1.2 MeV
	Photons/pulse	N_γ	$\sim 10^7$
	Peak on axis brilliance	B_x	$\sim 1 \times 10^{19}$ photons s^{-1}-mm^{-2}-mrad^{-2} (per 0.1% BW)



A real application: a platform for 4D cardiac microtomography of small rodents

Motivations (better deepened in talk by D. Panetta): technological challenges due to the required time/space resolution required

X-ray source	Spot size	Pulse duration	Allows in-line phase contrast	Prosp. gating	Retrosp. gating	Notes	refs
Minifocus tubes	30–200 μm	Continuous			•	Temporal resolution limited by the max. frame rate of X-ray detectors	47,66
Medical tubes	300–800 μm	$>$5 ms		•	•	Only with low magnification/ Sub-optimal spectral quality for small animal imaging	48,67
Carbon nanotube field emission X-ray tubes	$>$100 μm	$>$100 μs		•	•		68
Synchrotron hard X-ray beamlines (3rd generation)	Parallel beam	10–100 ps	•		•	4D CT *in-vivo* studies so far only applied to lung imaging/ few facilities	69,70
RF-based Thomson scattering	$>$40 μm	10–20 ps	•		•	No cardiac 4D imaging studies reported so far	13
All-optical Thomson scattering (this work)	$<$10 μm	$<$100 fs	•		•		—



Aiming at providing a compact and affordable source to be disseminated over small-scale laboratories

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A platform for 4D cardiac microtomography of small rodents
Main figures

Parameters safely attainable with a 100TW class laser system (75TW used for the LWFA beam)

Thomson scattering X-ray source parameters		Imaging simulation parameters	
Electron bunch		SAD	1000 mm
Size	$2\,\mu$m $\times$ $2\,\mu$m (tr), $3\,\mu$m (long)	ADD	1500 mm
Divergence	10 mrad	Magnification	2.5
Bunch charge	100 pC	Detector size (transverse $\times$ axial)	$50 \times 25\,\text{mm}^2$
Mean energy	~50 MeV	Detector pixel size	$250\,\mu$m
Energy spread	$\lesssim 20\%$ rms	X-ray pulse duration	0
Scattering laser pulse		Total n. of X-ray pulses (for the entire 4D reconstruction)	6000 to 24000
Duration	500 fs (chirped)	Unattenuated no. photons per $250\,\mu$m pixel	5000
Energy	1 J	Unattenuated no. photons per $50\,\mu$m pixel	200
Central wavelength	800 nm	Size of the cubic voxel in tomographic reconstructions	$100\,\mu$m
Spot size	$20\,\mu$m		
a_0	~0.24		
X-ray source			
Duration	~10 fs		
Source transverse size	$2\,\mu$m $\times$ $2\,\mu$m		
No. of photons within 10 mrad per laser shot	$\sim 9.8 \times 10^7$		

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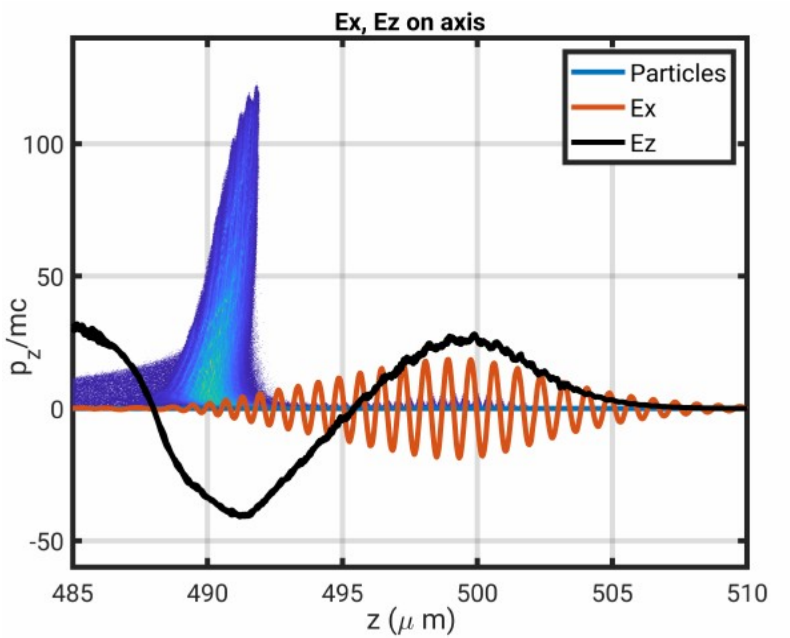
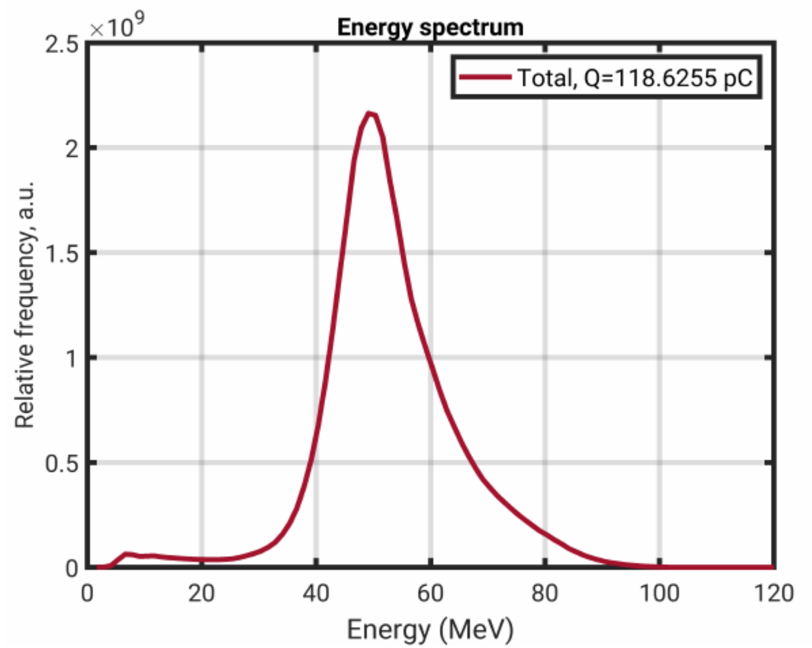
D. Panetta, L. Labate *et al.*, Sci. Rep. **9**, 8439 (2019)

A platform for 4D cardiac microtomography of small rodents
The LWFA regime

The LWFA process was simulated using the PIC code "FBPIC"
"Not so narrow" energy spectrum required → 15-20% electron energy spread
Moderate focusing: $a_0 \sim 1.6$
Ionization injection on a mixture He-N_2

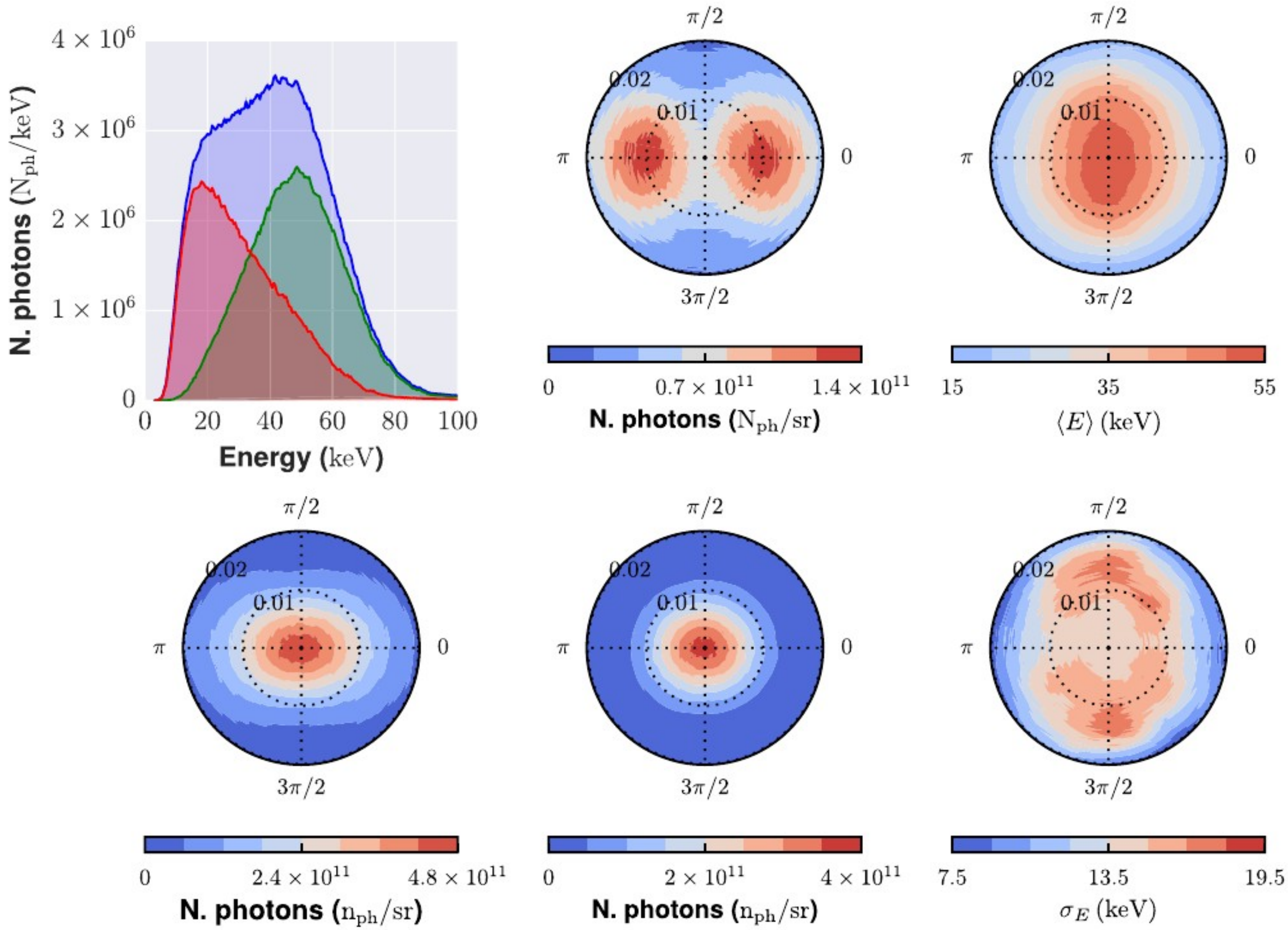




D. Panetta, L. Labate *et al.*, Sci. Rep. **9**, 8439 (2019)

A platform for 4D cardiac microtomography of small rodents
The final X-ray beam

Thomson Scattering process simulated using the TSST code*



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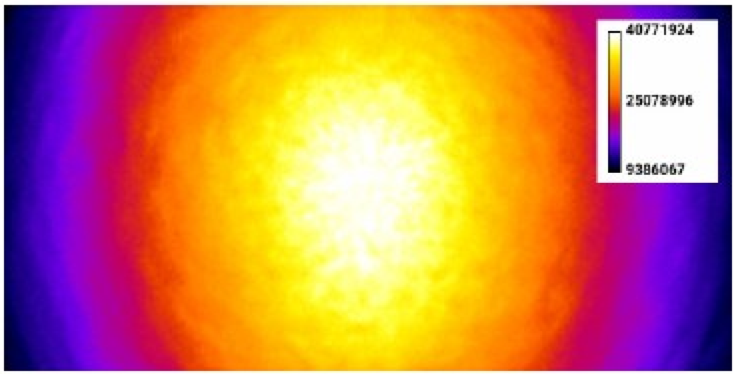
*P. Tomassini *et al*, Appl. Phys. B **80**, 419 (2005)

A platform for 4D cardiac microtomography of small rodents
Monte Carlo simulation of the imaging capabilities

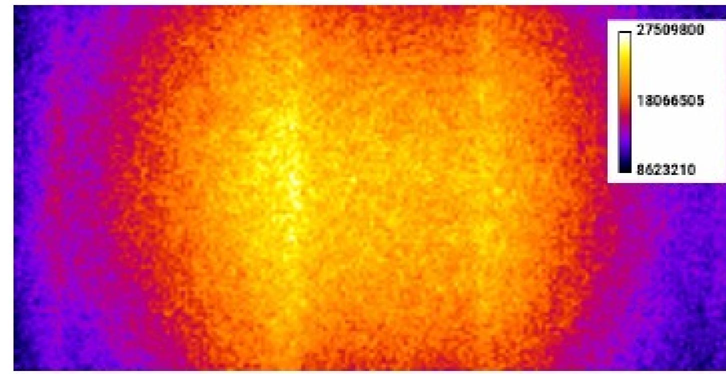
Imaging capabilities simulated using the "real" spectrum using GEANT4

Energy deposited on a GADOX screen (100micron thickness)

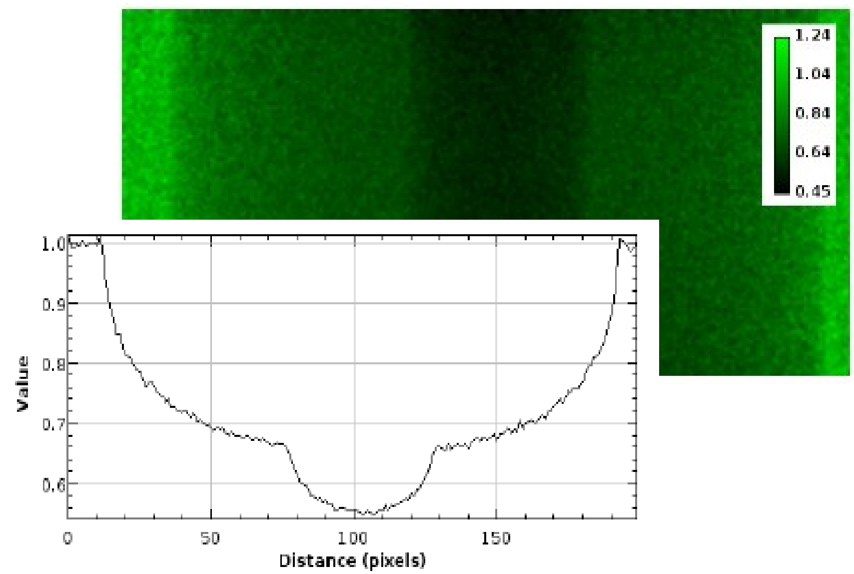


Number of photons impinging on each (250x250 micron2) "pixel"

Numerical simulation radiography of a cylinder (+iodinated insert) phantom



Flat-field corrected



*P. Tomassini *et al*, Appl. Phys. B **80**, 419 (2005)

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Summary and conclusions

- Laser-driven e- acceleration already mature for direct e-beam applications in medicine and for driving secondary sources
- First demonstration experiment of advanced RT modalities with laser-driven e- bunches
- Accurate dosimetry first performed: PDD z_{max}~35mm, $z_{50\%}$~80-100mm, D at z_{max} ~3-5cGy/shot (relevance for pediatric or head/neck tumors)
- Advanced RT modalities with LWFA "pencil" beams: Intensity Modulated RT and multi-field irradiation
- Dose up to ~2.5Gy (using ~200 laser shots) delivered to a 5mm size volume at ~50mm depth
  Dose goes to ~0.1 of the maximum a few mm away from the target volume
- Demonstration of transverse dose tailoring with mm resolution
- Perspectives for reaching a "FLASH therapy regime" in the medium term
- Issues: improve e- spectral features (get rid of low-energy components) to enhance ratio of doses to the target volume to dose to the entrance volumes, pointing stability issues, ...
- Studies toward all-optical (compact, affordable, ...) advanced X-ray sources for applications in medicine
- Promising feasibility study of a microCT platform of small animals
- Exciting perspectived for phase-contrast imaging

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